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(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS

(57) Abstract

Non–peptide compounds comprising a central hydrazide motif and methods for the synthesis thereof. The compounds act to antagonize the action of the glucagon peptide hormone.

*(Referred to in PCT Gazette No. 19/1999, Section II)

GLUCAGON ANTAGONISTS/INVERSE AGONISTS

Field of the invention

The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. It relates particularly to non-peptide glucagon antagonists or inverse agonists.

Background of the invention

Glucagon is a key hormonal agent that, in cooperation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposed by insulin which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.

Glucagon is produced in the alpha islet cells and insulin in the beta islet cells of the pancreas. Diabetes mellitus, the common disorder of glucose metabolism, is characterized by hyperglycemia, and can present as type I, insulin-dependent, or type II, a form that is non-insulin-dependent in character. Subjects with type I diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with type I or II diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy animals as well as in animal models of type I and II, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al. Diabetologia 37, 985 (1994); Diabetes 43, [suppl 1], 172A (1994); Am J Physiol 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action antagonistic to glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, substances that inhibit or prevent glucagon induced response. The antagonist can be peptide or non-peptide in nature. Native glucagon is a 29 amino acid-containing peptide having the sequence:

Description of the invention

Definitions

The following is a detailed definition of the terms used to describe the compounds of the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

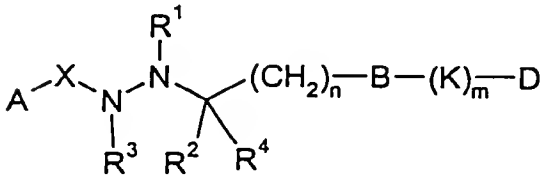
The term "alkyl" in the present context designates a hydrocarbon chain or a ring that is either saturated or unsaturated (containing one or more double or triple bonds where feasible) of from 1 to 10 carbon atoms in either a linear or branched or cyclic configuration. Thus, alkyl includes for example n-octyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, allyl, propargyl, 2-hexynyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, cyclooctyl, 4-cyclohexylbutyl, and the like.

Further non-limiting examples are *sec*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl, n-heptyl, n-nonyl, n-decyl, vinyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 2,4-heptadienyl, 1-octenyl, 2,4-octadienyl, ethynyl, 1-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-hepynyl, 1-octynyl, 2-decynyl, cyclobutyl, cyclopentyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclohexenylmethyl, 4-cyclohexyl-2-butenyl, 4-(1-cyclohexenyl)-vinyl and the like.

The term "lower alkyl" designates a hydrocarbon moiety specified above, of from 1 to 6 carbon atoms.

"Aryl" means an aromatic ring moiety, for example: phenyl, naphthyl, furyl, thienyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazolyl, imidazolyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,

Accordingly, the invention is concerned with compounds of the general formula I:



(I)

wherein:

R^1 and R^2 independently are hydrogen or lower alkyl or together form a valence bond;

R^3 and R^4 independently are hydrogen or lower alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

X is >C=O, >C=S, >C=NR^5 or >SO_2;

wherein R^5 is hydrogen, lower alkyl, aryl-lower alkyl or -OR^6;

wherein R^6 is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

A is

R^7 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SO_2NR^{11}R^{12}$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-OCH_2CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$ or $-OSO_2CF_3$;

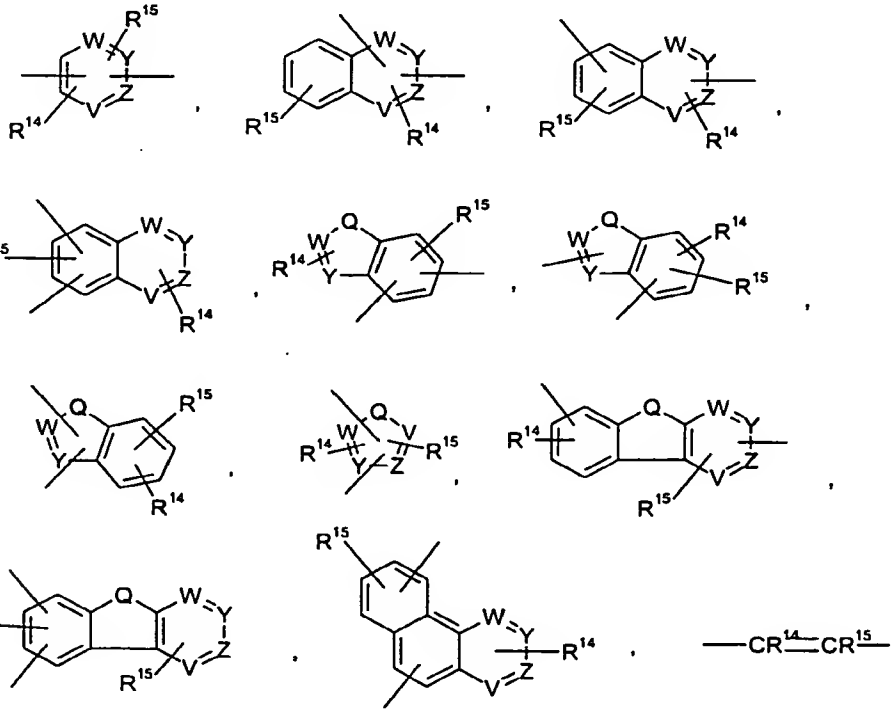
R^8 and R^9 independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, $-SCF_3$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$ or $-OSO_2CF_3$, or R^8 and R^9 together form a bridge $-OCH_2O-$ or $-OCH_2CH_2O-$;

wherein R^{11} and R^{12} independently are hydrogen, $-COR^{13}$, $-SO_2R^{13}$, lower alkyl or aryl;

wherein R^{13} is hydrogen, lower alkyl, aryl-lower alkyl or aryl; and

R^{10} is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

B is



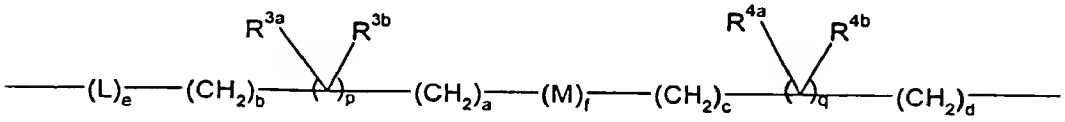
or a valence bond;

wherein R^{24} and R^{25} independently are hydrogen, $-COR^{26}$, $-SO_2R^{26}$, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{26} is hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

R^{23} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



wherein:

R^{3a}, R^{3b}, R^{4a} and R^{4b} independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{24a}$, $-NR^{24a}R^{25a}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SR^{24a}$, $-CHF_2$, $-OCHF_2$, $-OCF_2CHF_2$, $-OSO_2CF_3$, $-CONR^{24a}R^{25a}$, $-CH_2CONR^{24a}R^{25a}$, $-OCH_2CONR^{24a}R^{25a}$, $-CH_2OR^{24a}$, $-CH_2NR^{24a}R^{25a}$, $-OCOR^{24a}$ or $-CO_2R^{24a}$;

wherein R^{24a} and R^{25a} independently are hydrogen, $-COR^{26a}$, $-SO_2R^{26a}$, lower alkyl, aryl or aryl-lower alkyl;

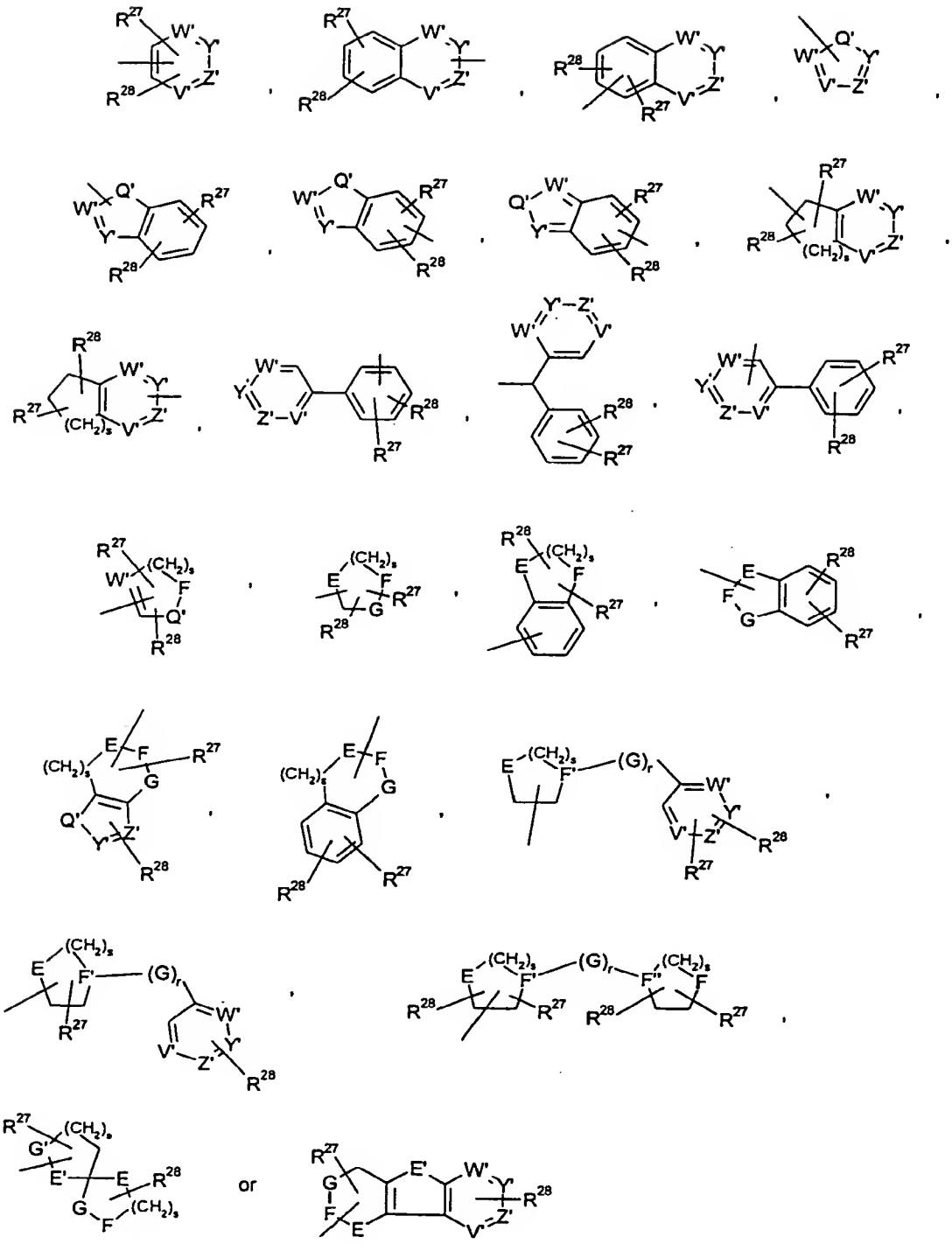
wherein R^{26a} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, or R^{3a} and R^{4b} together form a bridge $-(CH_2)_i-$;

wherein i is 1, 2, 3 or 4;

a, b, c and d independently are 0, 1, 2, 3 or 4;



wherein:

r is 0 or 1;

wherein R^{31} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

R^{36} and R^{39} independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

R^{38} is hydrogen, $-OR^{40}$, $-NR^{40}R^{41}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SR^{40}$, $-CHF_2$, $-OCHF_2$, $-OCF_2CHF_2$, $-CONR^{40}R^{41}$, $-(CH_2)_xCONR^{40}R^{41}$, $-O(CH_2)_xCONR^{40}R^{41}$, $-(CH_2)_xOR^{40}$, $-(CH_2)_xNR^{40}R^{41}$, $-OCOR^{40}$ or $-CO_2R^{40}$;

wherein x is 1, 2, 3 or 4;

R^{40} and R^{41} independently are hydrogen, $-COR^{42}$, $-SO_2R^{42}$, lower alkyl, aryl or aryl-lower alkyl;

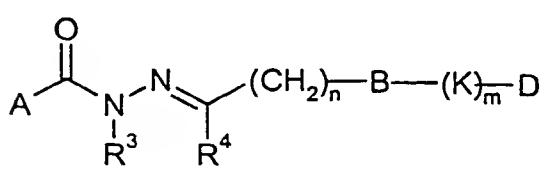
wherein R^{42} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

Where the formulae for B make it possible, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} may alternatively be replaced by R^{14} or R^{15}, respectively. In such case eg W may be selected from -N=, $-CR^{19}$- and $-CR^{14}$-.

Similarly, where the formulae for D make it possible, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{38} and R^{39} may alternatively be replaced by R^{27} or R^{28}, respectively. In such case eg E may be selected from $-CHR^{38}$-, >C=O, $>NR^{39}$, -O-, -S-, $-CHR^{27}$- and $>NR^{27}$.

In a preferred embodiment the invention relates to compounds of the following general formula II:

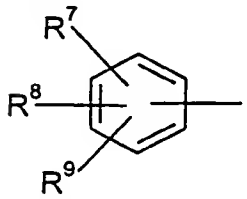


(II)

wherein A, B, K, D, R^3, R^4, n and m are as defined for formula I.

wherein R^7, R^8, R^9 and R^{10} are as defined for formula I.

A is more preferably



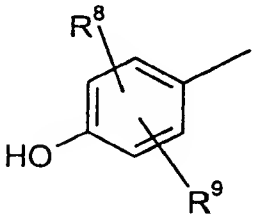
wherein R^7, R^8 and R^9 are as defined for formula I.

In the above embodiments of A, R^7 is preferably halogen, lower alkyl, -OH, $-NO_2$, -CN, $-CO_2H$, -O-lower alkyl, aryl, aryl-lower alkyl, $-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ or $-OCF_3$.

Preferably, R^8 and R^9 are independently hydrogen, halogen, -OH, $-NO_2$, $-NH_2$, -CN, $-OCF_3$, $-SCF_3$, $-CF_3$, $-OCH_2CF_3$, -O-lower alkyl such as methoxy and ethoxy, lower alkyl such as methyl and ethyl, or phenyl, and R^{10} is hydrogen, lower alkyl or phenyl.

More preferably, R^8 and R^9 are independently selected from hydrogen, halogen such as -F and -Cl, -O-lower alkyl such as methoxy and ethoxy, $-NH_2$, -CN or $-NO_2$, and R^{10} is hydrogen.

In a particularly preferred embodiment A is



wherein R^8 and R^9 independently are hydrogen, halogen, -OH, $-NO_2$, $-NH_2$, -CN, $-OCF_3$, $-SCF_3$, $-CF_3$, $-OCH_2CF_3$, -O-lower alkyl such as methoxy and ethoxy, lower alkyl such as methyl and ethyl, or phenyl, preferably hydrogen, halogen such as -F and -Cl, -O-lower alkyl such as methoxy and ethoxy, $-NH_2$, -CN or $-NO_2$.

In a further particularly preferred embodiment A is

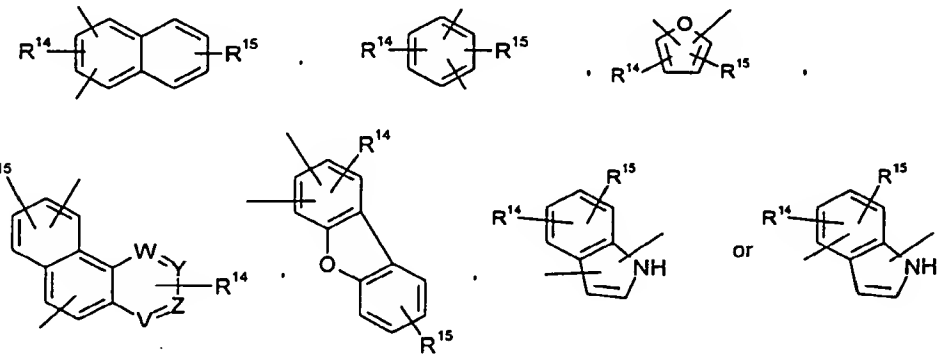
wherein V, W, Z, Y and Q are as defined for formula I; and

R^{14} and R^{15} independently are hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{16}$, $-NR^{16}R^{17}$, lower alkyl, aryl, aryl-lower alkyl, $-OSO_2CF_3$, $-CONR^{18}R^{17}$, $-CH_2OR^{18}$, $-CH_2NR^{16}R^{17}$, $-OCOR^{16}$ or $-CO_2R^{18}$; or R^{14} and R^{15} together form a bridge $-OCH_2O-$ or $-(CH_2)_l-$;

wherein l, R^{16}, R^{17} and R^{18} are as defined for formula I.

Q is preferably -O- or -NH-.

Particularly preferred compounds are those in which B is



wherein V, W, Z, Y and Q are as defined for formula I; and

R^{14} and R^{15} independently are hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{18}$, $-NR^{16}R^{17}$, lower alkyl, aryl, aryl-lower alkyl, $-OSO_2CF_3$, $-CONR^{16}R^{17}$, $-CH_2OR^{16}$, $-CH_2NR^{16}R^{17}$, $-OCOR^{16}$ or $-CO_2R^{18}$; or R^{14} and R^{15} together form a bridge $-OCH_2O-$ or $-(CH_2)_l-$;

wherein l, R^{16}, R^{17} and R^{18} are as defined for formula I.

Still more preferred are compounds of the following formula VI:

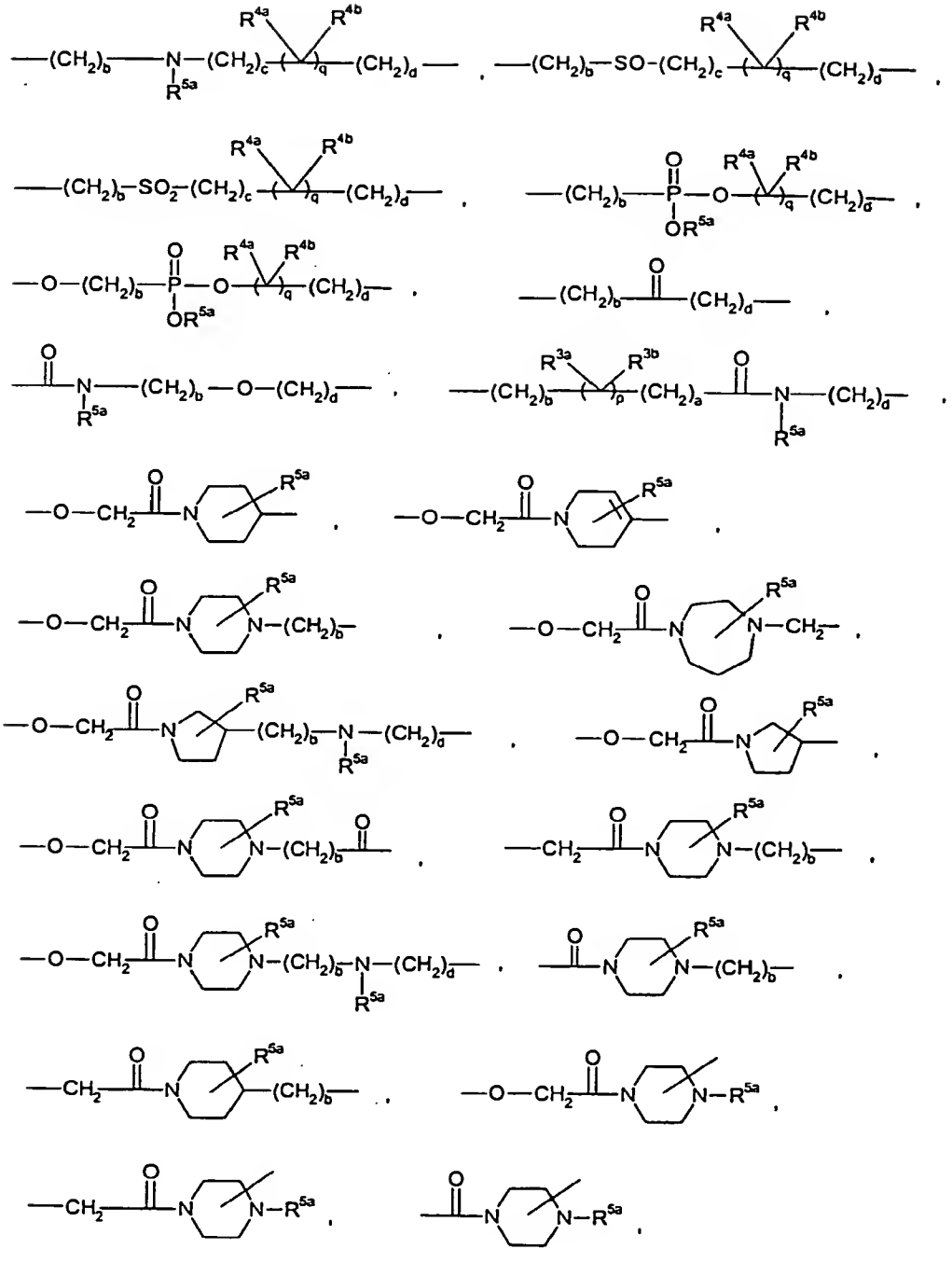
K, D and m are as defined for formula I; and

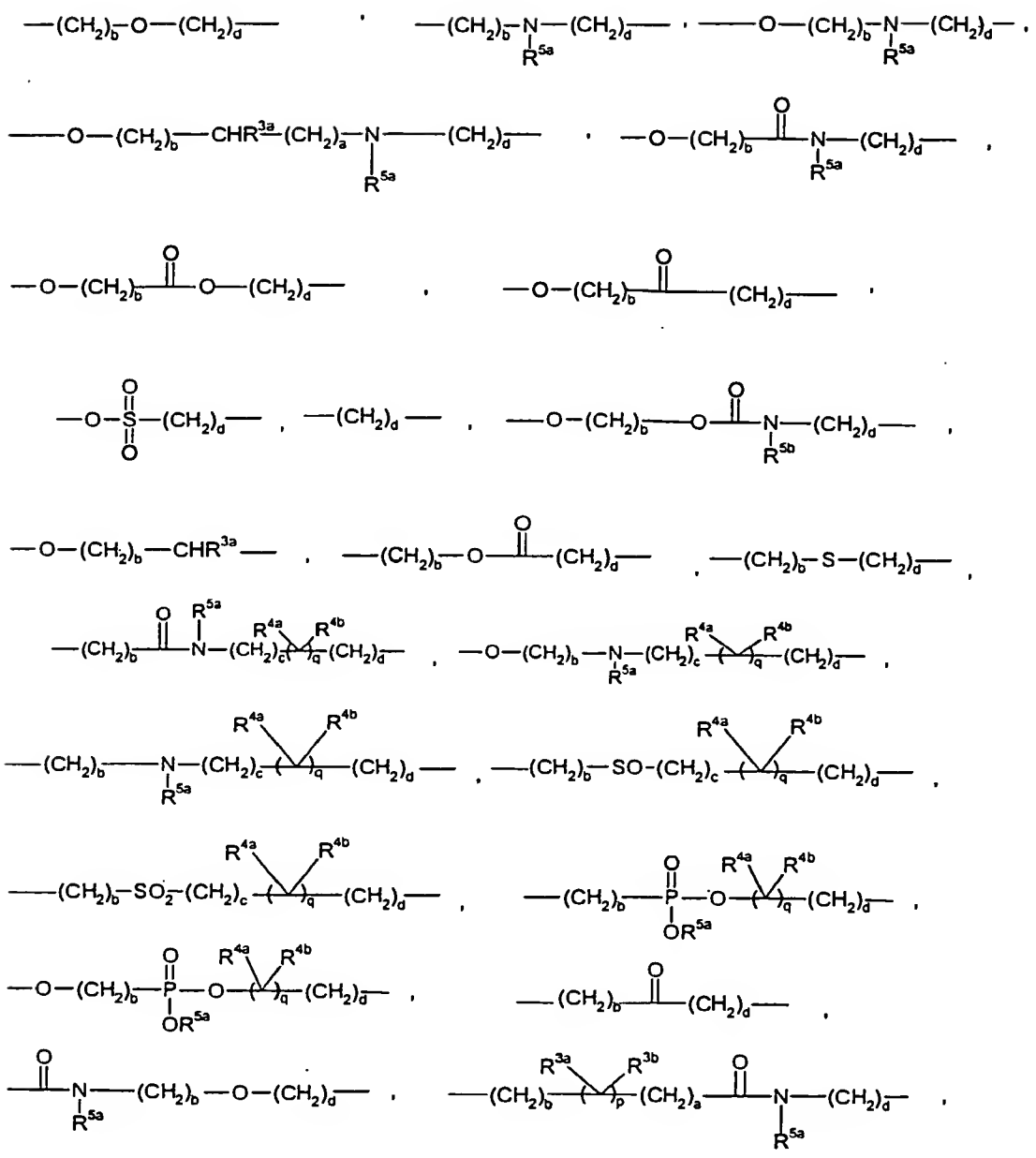
R^8 and R^9 are as defined for formula I and preferably as defined for the preferred embodiments of A above.

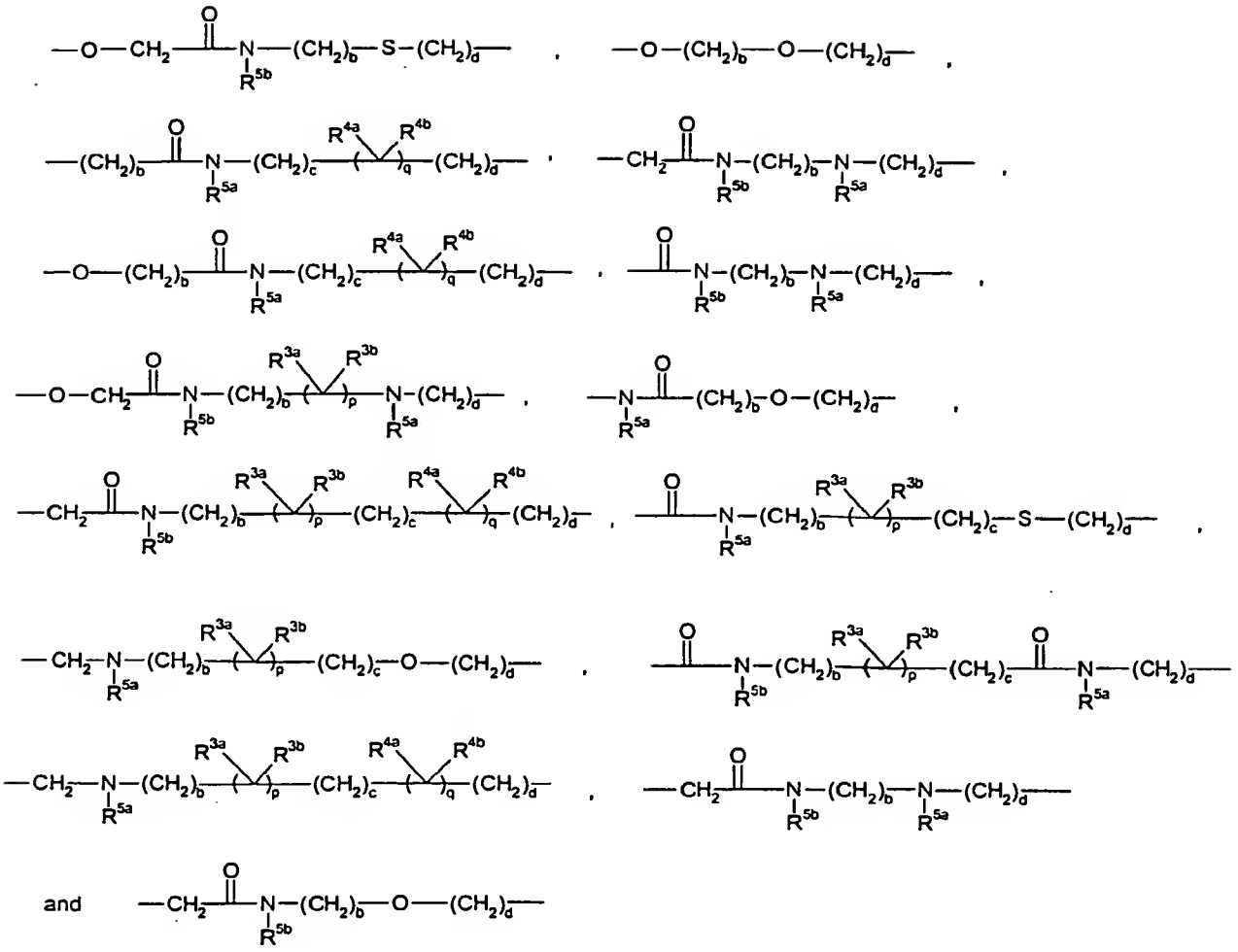
In the above formulae VI, VII and VIII, R^{14} and R^{15} are preferably independently hydrogen, halogen, lower alkyl, aryl such as phenyl, or -O-lower alkyl such as methoxy.

In the above formulae VI and VII, K is preferably bound in para-position and in the above formulae VIIIa and VIIIb, K is preferably bound at the nitrogen atom of the indole group.

K is preferably selected from the group consisting of:

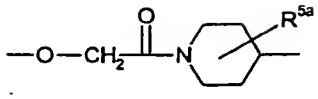
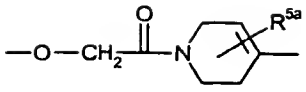
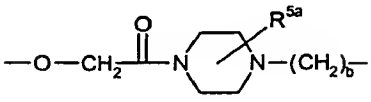
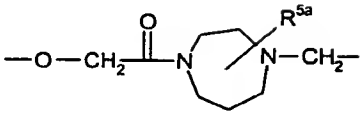
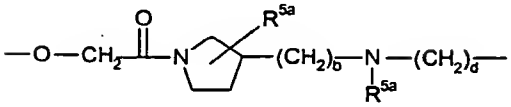
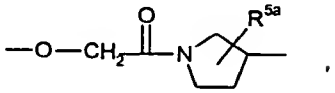
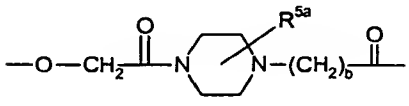
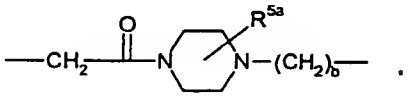
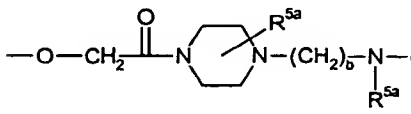
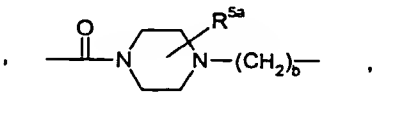


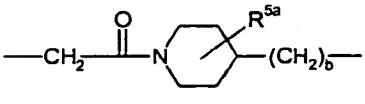
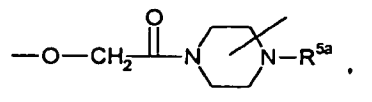
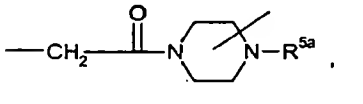
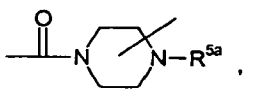




wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, a, b, c, d, p and q are as defined for formula I.

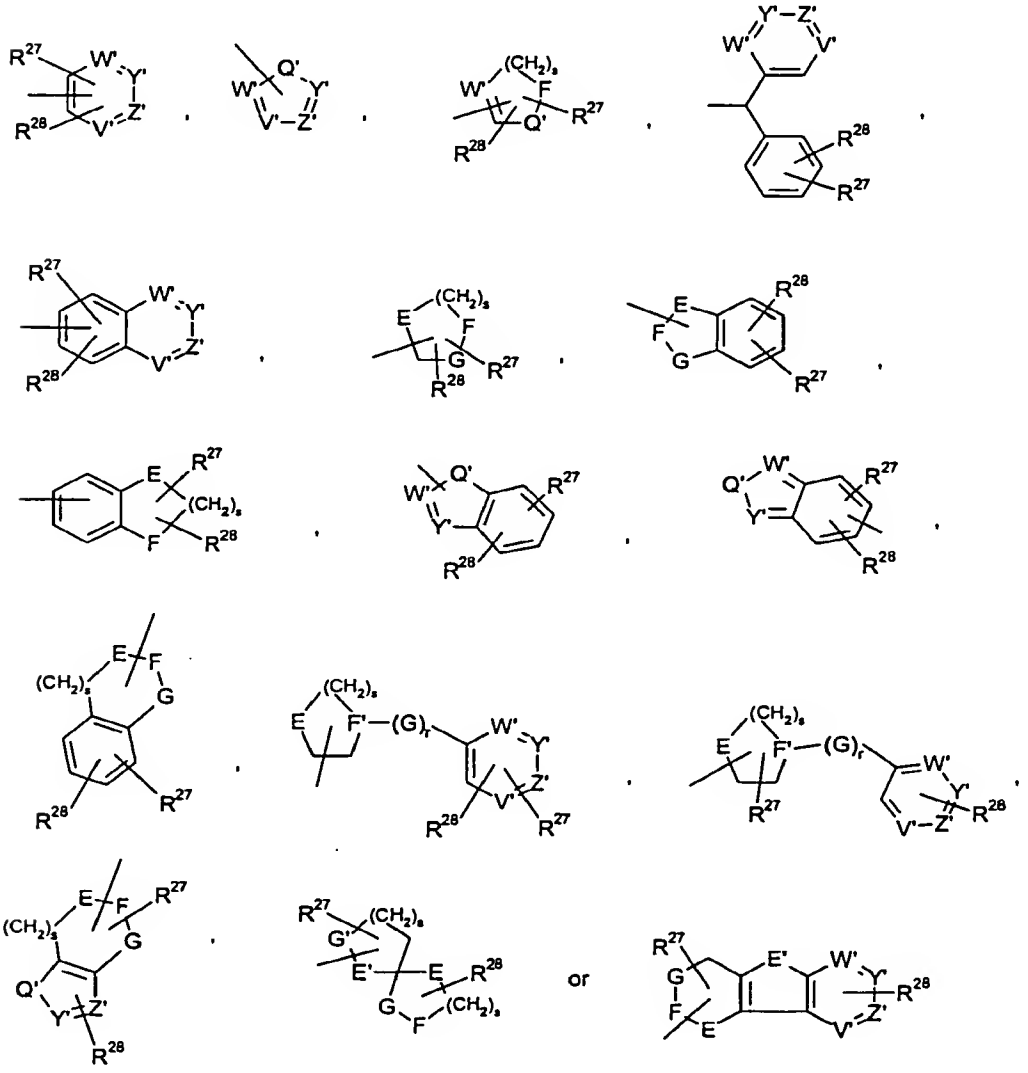
In a further preferred embodiment K is selected from the group consisting of:

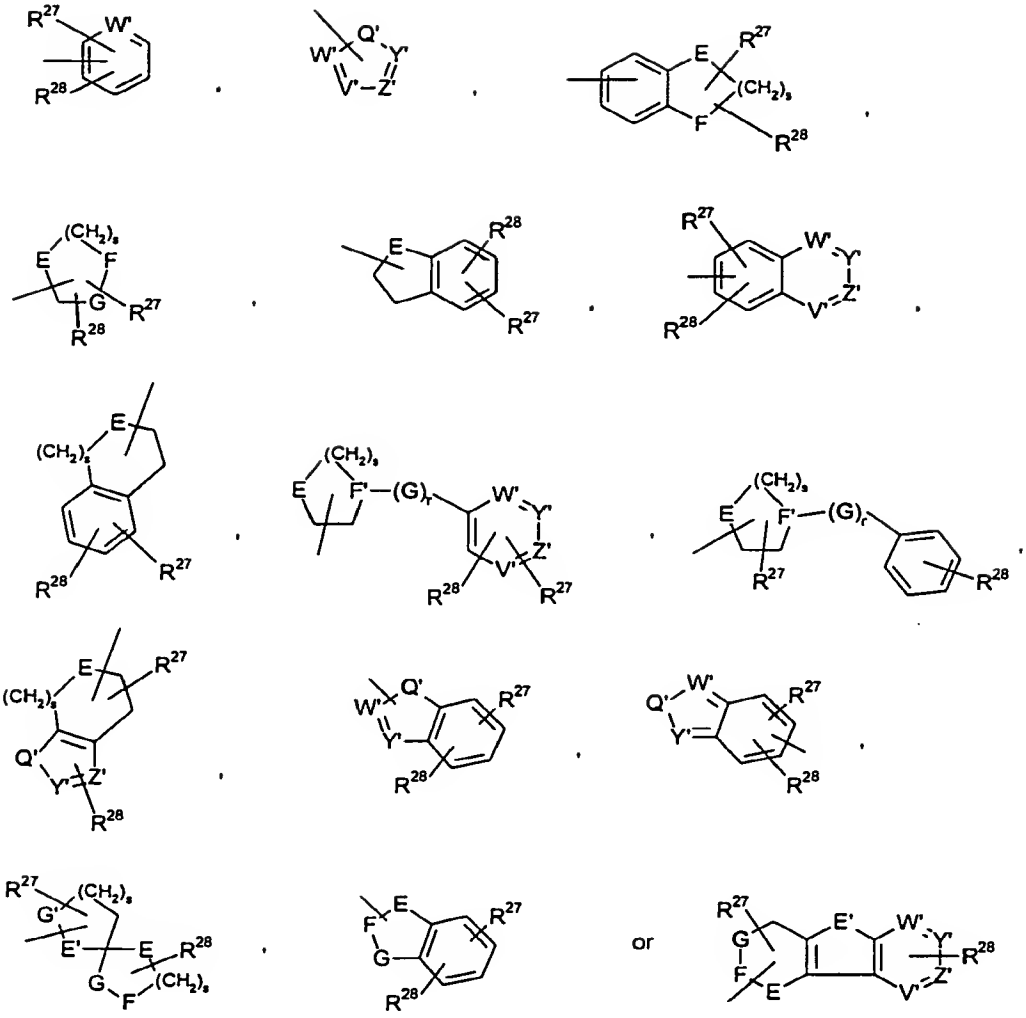
In the above embodiments of K, R^{4a} and R^{4b} are preferably independently hydrogen, -CN, $-CONH_2$, $-(CH_2)-N(CH_3)_2$, -O-lower alkyl, $-CH_2OH$, $-CH_2O$-aryl, $-N(CH_3)_2$, -OH, $-CO_2$-lower alkyl or lower alkyl.

D is preferably hydrogen,



wherein s, r, R^{27}, R^{28}, V', Y', Q', Z', W', E, E', F, F', G and G' are as defined for formula I.

In still a further preferred embodiment D is hydrogen,



wherein E and E' independently are >CHR^{38}, >NR^{39} or -O-; F, G and G' independently are >CHR^{38}, >C=O or >NR^{39}; F' is >CR^{38}- or >N-; and s, r, R^{27}, R^{28}, R^{38}, R^{39}, V', Y', Z', Q' and W' are as defined for formula I.

R^{27} and R^{28} are preferably independently hydrogen; halogen such as -Cl, -Br or -F; -CF_3; -OCF_3; -$OCHF_2$; -OCH_2CF_3; -$(CH_2)_yNHCOCF_3$; -$NHCOCF_3$; -CN; -NO_2; -COR^{29}, -$COOR^{29}$, -$(CH_2)_yOR^{29}$ or -OR^{29} wherein R^{29} is hydrogen, aryl or lower alkyl and y is 1, 2, 3 or 4; lower alkyl such as methyl, ethyl, 2-propenyl, isopropyl, tert-butyl or cyclohexyl; lower alkylthio; -SCF_3; aryl such as phenyl; -$(CH_2)_yNR^{29}R^{30}$ or -$NR^{29}R^{30}$ wherein R^{29} and R^{30} independently are hydrogen, -COO-lower alkyl or lower alkyl and y is 1, 2, 3 or 4; or -$CONH_2$; or R^{27}and R^{28} together form a bridge -OCH_2O-; R^{38} is hydrogen; -$OCHF_2$; -OR^{40} wherein R^{40} is hydrogen or

In a further embodiment the invention relates to the compounds of the formula I wherein:

R^1 and R^2 independently are hydrogen or lower alkyl or together form a valence bond;

R^3 and R^4 independently are hydrogen or lower alkyl;

X is >C=O, >C=S, >C=NR^5 or >SO_2;

n is 0, 1, 2 or 3;

m is 0 or 1;

R^5 is hydrogen, lower alkyl, aryl-lower alkyl, or -OR^6;

wherein R^6 is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

A is

R^7 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, $-SCF_3$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$, $-OSO_2CF_3$;

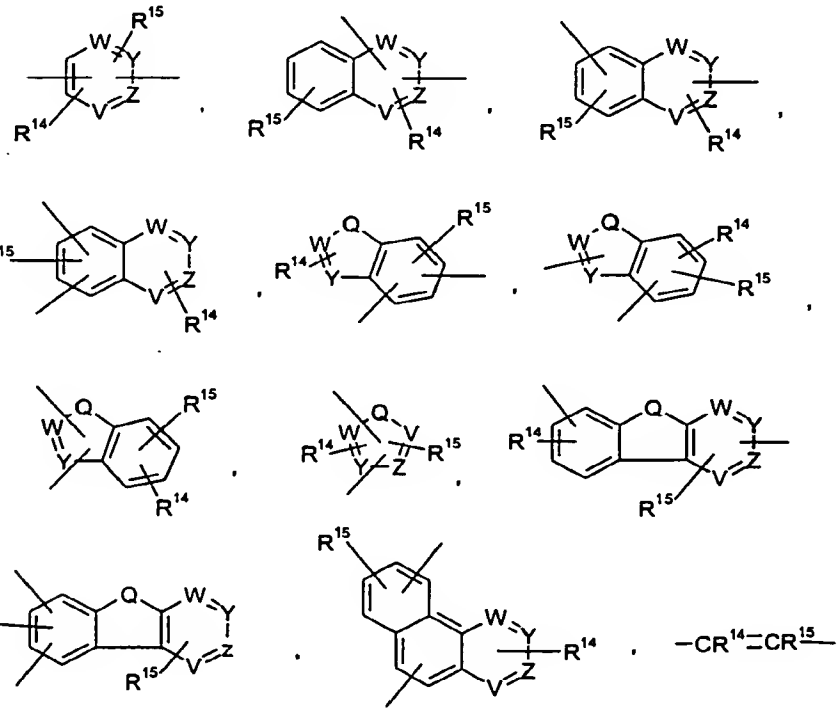
R^8 and R^9 independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, $-SCF_3$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$, $-OSO_2CF_3$, or R^8 and R^9 together form a bridge $-OCH_2O-$;

R^{11} and R^{12} independently are hydrogen, $-COR^{13}$, $-SO_2R^{13}$, lower alkyl or aryl;

R^{13} is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

R^{10} is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

B is



or a valence bond; preferably

Z is -N= or -CR^{21}=;

V is -N= or -CR^{22}=;

Q is -NR^{23}-, -O- or -S-;

wherein:

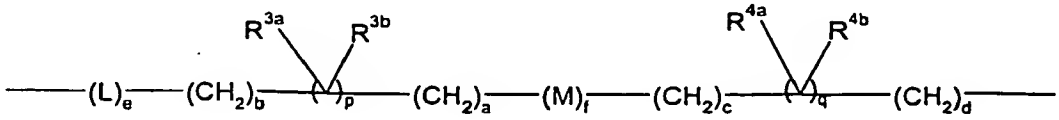
R^{19}, R^{20}, R^{21} and R^{22} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -NO_2, -OR^{24}, -$NR^{24}R^{25}$, lower alkyl, aryl, aryl-lower alkyl, SCF_3, -SR^{24}, -CHF_2, -$OCHF_2$, OCF_2CHF_2, -OSO_2CF_3, -$CONR^{24}R^{25}$, -$CH_2CONR^{24}R^{25}$, -$OCH_2CONR^{24}R^{25}$, -CH_2OR^{24}, -$CH_2NR^{24}R^{25}$, -$OCOR^{24}$ or -CO_2R^{24}, or R^{19} and R^{20}, R^{20} and R^{21} or R^{21} and R^{22} together form a bridge -OCH_2O-;

R^{24} and R^{25} independently are hydrogen, -COR^{26}, -SO_2R^{26}, lower alkyl, aryl or aryl-lower alkyl;

R^{26} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

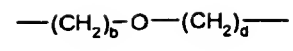
R^{23} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



wherein:

R^{3a}, R^{3b}, R^{4a} and R^{4b} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -NO_2, -OR^{24a}, -$NR^{24a}R^{25a}$, lower alkyl, aryl, aryl-lower alkyl, SCF_3, -SR^{24a}, -CHF_2, -$OCHF_2$, -OCF_2CHF_2, -OSO_2CF_3, -$CONR^{24a}R^{25a}$, -$CH_2CONR^{24a}R^{25a}$, -$OCH_2CONR^{24a}R^{25a}$, -CH_2OR^{24a}, -$CH_2NR^{24a}R^{25a}$, -$OCOR^{24a}$ or -CO_2R^{24a};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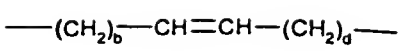
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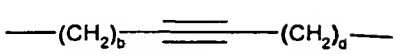
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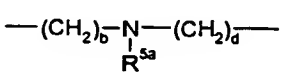
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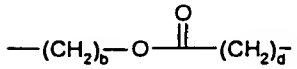
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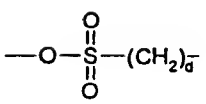
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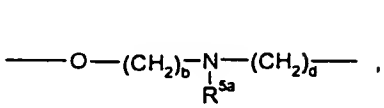
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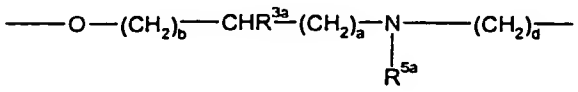
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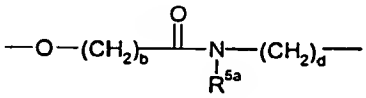
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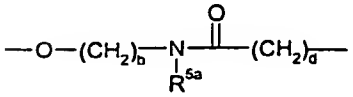
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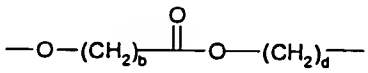
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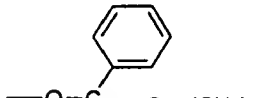
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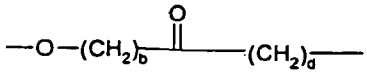


D is hydrogen or

Z' is -N= or -CR^{33}=;

V' is -N= or -CR^{34}=;

W' is -N= or -CR^{35}=;

Q' is -NR^{36}-, -O- or -S-;

wherein

R^{27}, R^{28}, R^{32}, R^{33}, $R^{34}$and R^{35} are independently hydrogen, halogen, -CN, -CF_3, -OCF_3, -$O(CH_2)_yCF_3$, -NO_2, -OR^{29}, -$NR^{29}R^{30}$, lower alkyl, aryl, aryl-lower alkyl, -SCF_3, -SR^{29}, -CHF_2, -$OCHF_2$, -OCF_2CHF_2, -OSO_2R^{29}, -OSO_2CF_3, -$CONR^{29}R^{30}$, -$(CH_2)_yCONR^{29}R^{30}$, -$O(CH_2)_yCONR^{29}R^{30}$, -$(CH_2)_yOR^{29}$, -$(CH_2)_yNR^{29}R^{30}$, -$OCOR^{29}$, -CO_2R^{29}; or $R^{27}$and R^{28}, R^{32} and R^{33}, R^{33} and R^{34} or R^{34} and R^{35} together form a bridge -OCH_2O-;

R^{27} and R^{28} preferably independently representing hydrogen, halogen,-CF_3, -OCF_3, -OCH_2CF_3, -OR^{29}, lower alkyl, aryl or aryl-lower alkyl, or together forming a bridge -OCH_2O-;

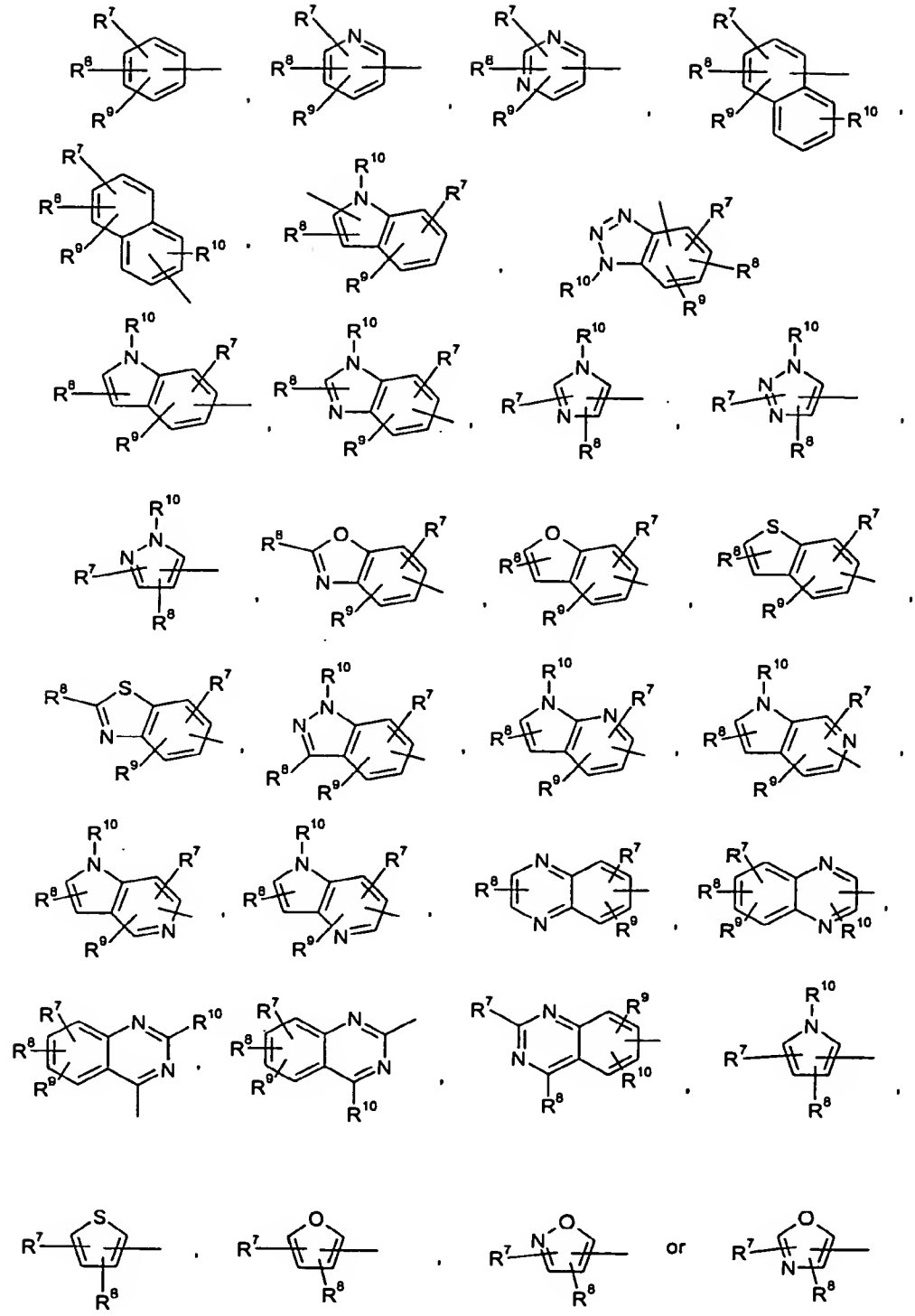
y is 1, 2, 3 or 4;

R^{29} and R^{30} independently are hydrogen, -COR^{31}, -SO_2R^{31}, lower alkyl, aryl or aryl-lower alkyl;

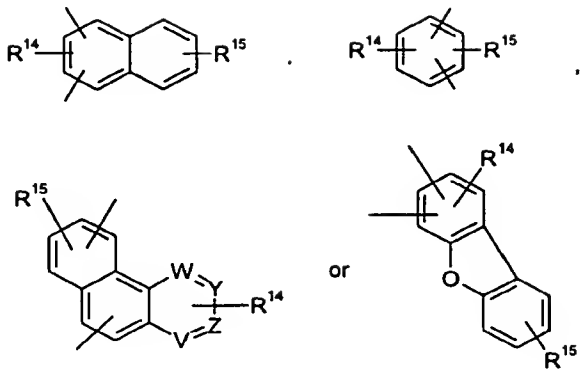
$R^{31}$is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

R^{36} and R^{39} independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl;

R^{38} is hydrogen, -OR^{40}, -$NR^{40}R^{41}$, lower alkyl, aryl, aryl-lower alkyl, -SCF_3, -SR^{40}, -CHF_2, -$OCHF_2$, -OCF_2CHF_2, -$CONR^{40}R^{41}$, -$(CH_2)_xCONR^{40}R^{41}$, -$O(CH_2)_xCONR^{40}R^{41}$, -$(CH_2)_xOR^{40}$, -$(CH_2)_xNR^{40}R^{41}$, -$OCOR^{40}$ or -CO_2R^{40};



wherein:



wherein:

R^{14} and R^{15} independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-O(CH_2)_lCF_3$, $-NO_2$, $-OR^{16}$, $-NR^{16}R^{17}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SR^{16}$, $-CHF_2$, $-OCHF_2$, $-OCF_2CHF_2$, $-OSO_2CF_3$, $-CONR^{16}R^{17}$, $-(CH_2)_lCONR^{16}R^{17}$, $-O(CH_2)_lCONR^{16}R^{17}$, $-(CH_2)_lCOR^{16}$, $-(CH_2)_lCOR^{16}$, $-(CH_2)_lOR^{16}$, $-O(CH_2)_lOR^{16}$, $-(CH_2)_lNR^{16}R^{17}$, $-O(CH_2)_lNR^{16}R^{17}$, $-OCOR^{16}$, $-CO_2R^{18}$, $-O(CH_2)_lCO_2R^{16}$, $-O(CH_2)_lCN$, $-O(CH_2)_lCl$, or R^{14} and R^{15} together form a bridge $-OCH_2O-$;

R^{14} and R^{15} preferably independently representing hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{16}$, $-NR^{16}R^{17}$, lower alkyl, aryl, aryl-lower alkyl, $-OSO_2CF_3$, $-CONR^{16}R^{17}$, $-CH_2OR^{16}$, $-CH_2NR^{16}R^{17}$, $-OCOR^{16}$ or $-CO_2R^{18}$; or together forming a bridge $-OCH_2O-$;

wherein l is 1, 2, 3 or 4;

R^{16} and R^{17} independently are hydrogen, $-COR^{16}$, $-SO_2R^{16}$, lower alkyl, aryl, or R^{16} and R^{17} together form a cyclic alkyl bridge containing from 2 to 7 carbon atoms;

wherein R^{18} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

W is -N= or $-CR^{19}$=;

Y is -N= or $-CR^{20}$=;

wherein R^{24a} and R^{25a} independently are hydrogen, $-COR^{26a}$, $-SO_2R^{26a}$, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{26a} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

or

R^{3a} and R^{3b}, R^{4a} and R^{4b} or R^{3a} and R^{4b} together form a bridge $-(CH_2)_i-$;

wherein i is 1, 2, 3 or 4;

a, b, c and d independently are 0, 1, 2, 3 or 4;

e, f and p independently are 0 or 1;

q is 0,1 or 2; and

L and M independently are

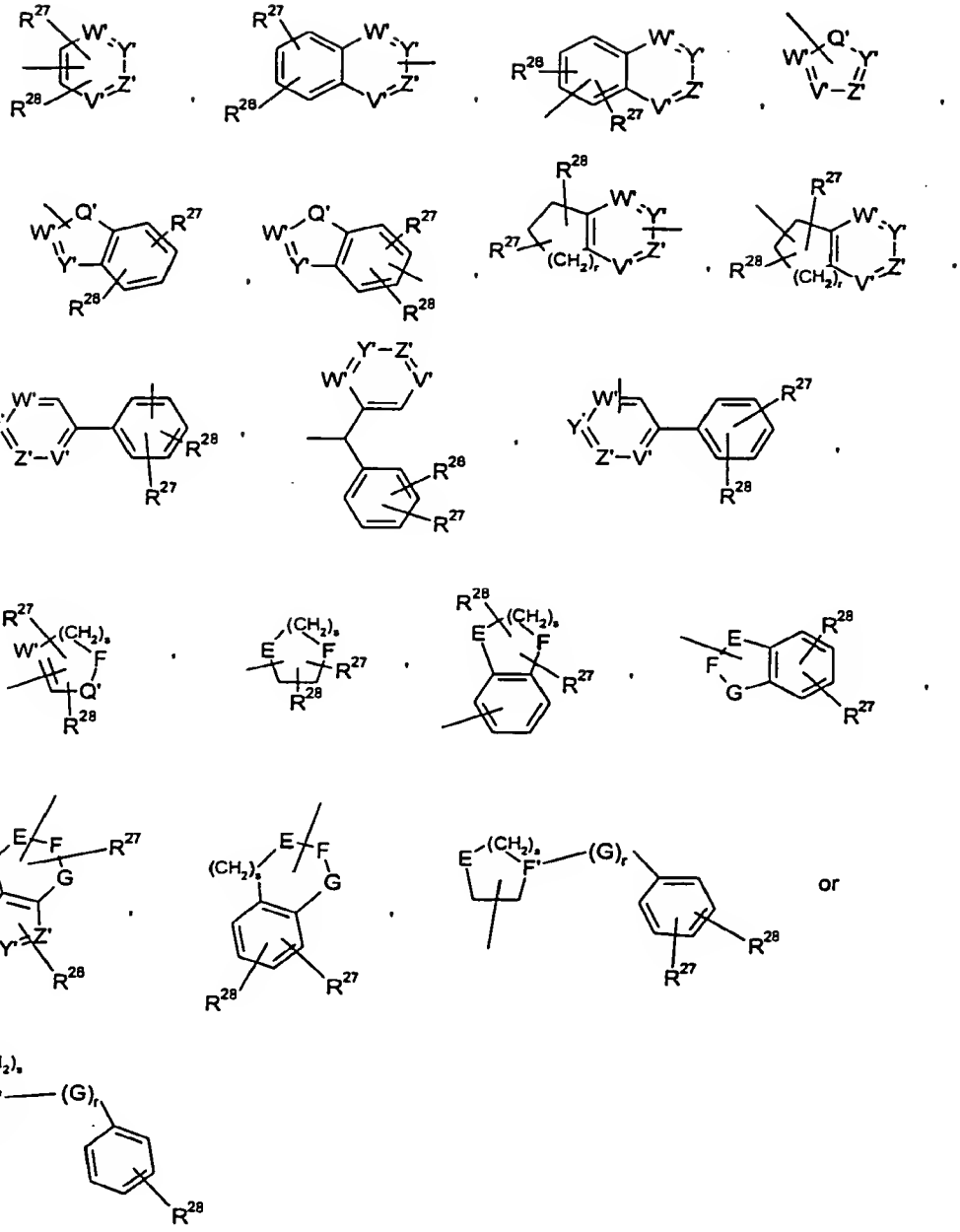
-O-, -S-, -CH=CH-, -C≡C-, $-NR^{5a}-$, -CO-, -OCO-, -COO-, $-CONR^{5a}-$, $-NR^{5a}CO-$, -SO-, $-SO_2-$, $-OSO_2-$, $-SO_2-NR^{5a}-$, $-NR^{5a}SO_2-$, $-NR^{5a}CONR^{5b}-$, $-NR^{5a}CSNR^{5b}-$, $-OCONR^{5b}-$ or $-NR^{5a}C(O)O-$;

wherein R^{5a} and R^{5b} independently are hydrogen, lower alkyl, $-(CH_2)_k-OH$, $-(CH_2)_k-NR^{6a}R^{6b}$, aryl or aryl-lower alkyl;

wherein k is 2, 3 or 4; and

R^{6a} and R^{6b} independently are hydrogen, lower alkyl or aryl-lower alkyl;

K preferably representing



or

preferably hydrogen,

W' is -N= or -CR^{35}=; and

Q' is -NR^{38}-, -O- or -S-;

wherein:

R^{27}, R^{28},R^{32}, R^{33}, $R^{34}$and R^{35} are independently hydrogen, halogen, -CN, -CF_3, -OCF_3, -$O(CH_2)_yCF_3$, -NO_2, -OR^{29}, -$NR^{29}R^{30}$, lower alkyl, aryl, aryl-lower alkyl, -SCF_3, -SR^{29}, -CHF_2, -$OCHF_2$, -OCF_2CHF_2, -OSO_2R^{29}, -OSO_2CF_3, -$CONR^{29}R^{30}$, -$(CH_2)_yCONR^{29}R^{30}$, -$O(CH_2)_yCONR^{29}R^{30}$, -$(CH_2)_yOR^{29}$, -$(CH_2)_yNR^{29}R^{30}$, -$OCOR^{29}$ or -CO_2R^{29};

or

$R^{27}$and R^{28}, R^{32} and R^{33}, R^{33} and R^{34} or R^{34} and R^{35} together form a bridge -OCH_2O-;

R^{27} and R^{28} preferably independently representing hydrogen; halogen such as -Cl or -F; -CF_3; -OCF_3; -$OCHF_2$; -OCH_2CF_3; -OR^{29} wherein R^{29} is hydrogen or lower alkyl; lower alkyl such as methyl, isopropyl or tert-butyl; lower alkylthio; -SCF_3; -CH_2OH; -COO-lower alkyl; aryl or -$CONH_2$; or together forming a bridge -OCH_2O-;

wherein y is 1, 2, 3 or 4; and

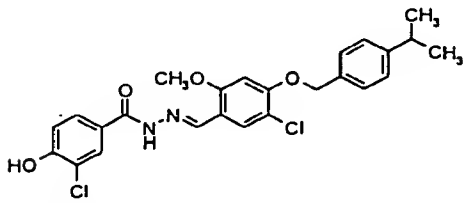
R^{29} and R^{30} independently are hydrogen, -COR^{31}, -SO_2R^{31}, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{31} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

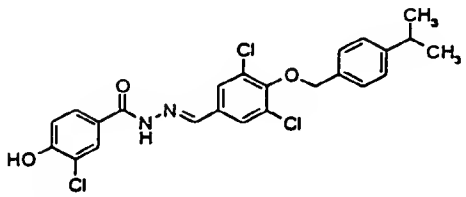
R^{36} and R^{39} independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

R^{38} is hydrogen, -OR^{40}, -$NR^{40}R^{41}$, lower alkyl, aryl, aryl-lower alkyl, -SCF_3, -SR^{40}, -CHF_2, -$OCHF_2$, -OCF_2CHF_2, -$CONR^{40}R^{41}$, -$(CH_2)_xCONR^{40}R^{41}$, -$O(CH_2)_xCONR^{40}R^{41}$, -$(CH_2)_xOR^{40}$, -$(CH_2)_xNR^{40}R^{41}$, -$OCOR^{40}$ or -CO_2R^{40};

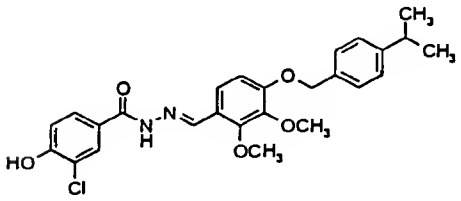
Examples of specific compounds represented by the above general formula V are the following:



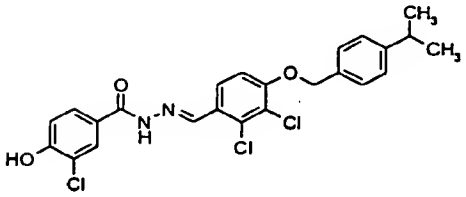
3-Chloro-4-hydroxybenzoic acid [5-chloro-2-methoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



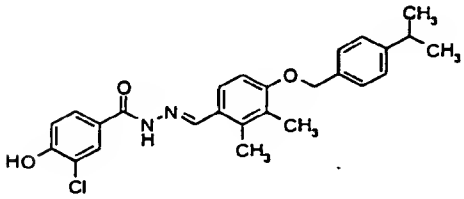
3-Chloro-4-hydroxybenzoic acid [3,5-dichloro-4-(4-isopropylbenzyloxy)benzylidene]hydrazide



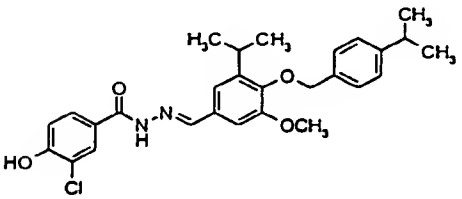
3-Chloro-4-hydroxybenzoic acid [2,3-dimethoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



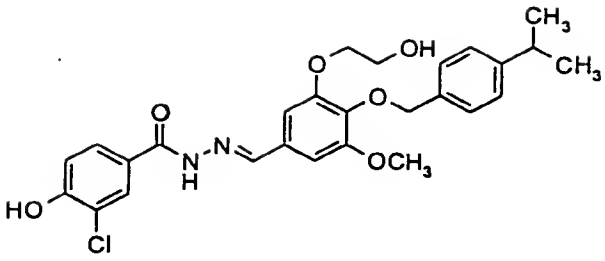
3-Chloro-4-hydroxybenzoic acid [2,3-dichloro-4-(4-isopropylbenzyloxy)benzylidene]hydrazide



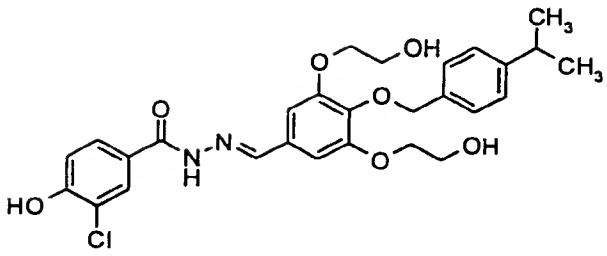
3-Chloro-4-hydroxybenzoic acid [2,3-dimethyl-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



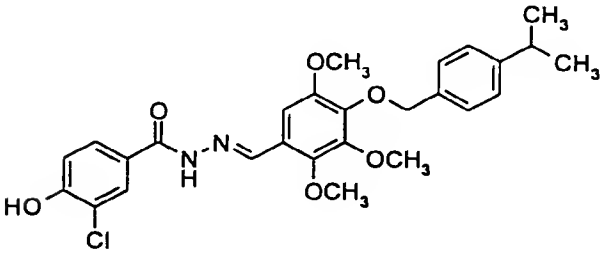
3-Chloro-4-hydroxybenzoic acid [3-isopropyl-4-(4-isopropylbenzyloxy)-5-methoxybenzylidene]hydrazide



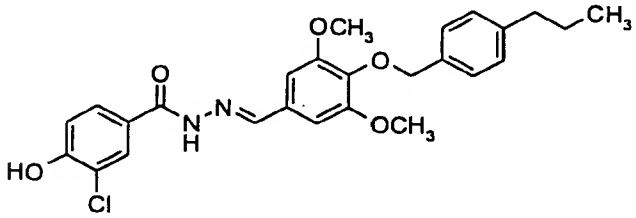
3-Chloro-4-hydroxybenzoic acid [3-(2-hydroxyethoxy)-4-(4-isopropyl-benzyloxy)-5-methoxybenzylidene]hydrazide



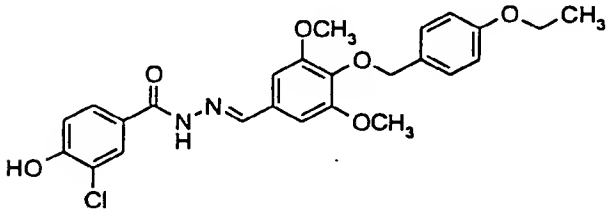
3-Chloro-4-hydroxybenzoic acid [3,5-bis-(2-hydroxyethoxy)-4-(4-isopropylbenzyloxy)benzylidene]hydrazide



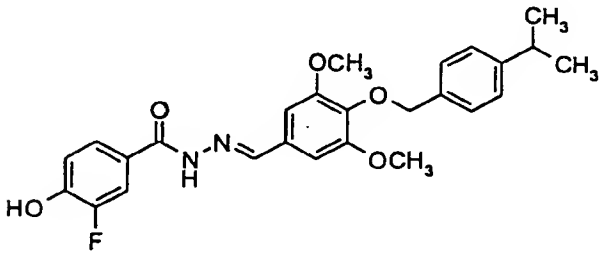
3-Chloro-4-hydroxybenzoic acid [2,3,5-trimethoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



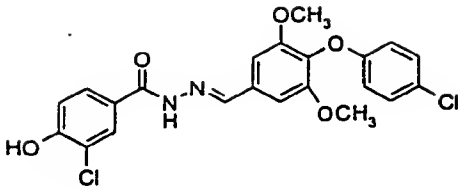
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-n-propylbenzyloxy)-benzylidene]hydrazide



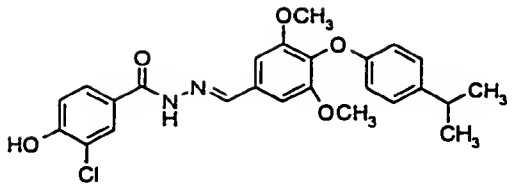
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-ethoxybenzyloxy)-benzylidene]hydrazide



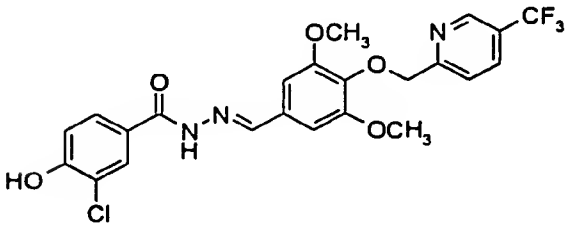
3-Fluoro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-isopropylbenzyloxy)-benzylidene]hydrazide



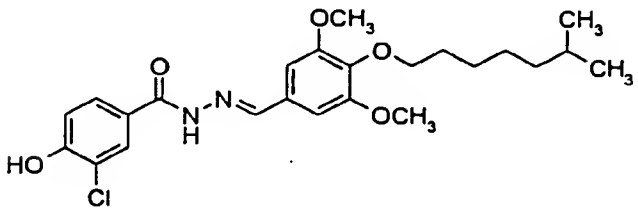
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-chlorophenoxy) benzylid-ene]hydrazide



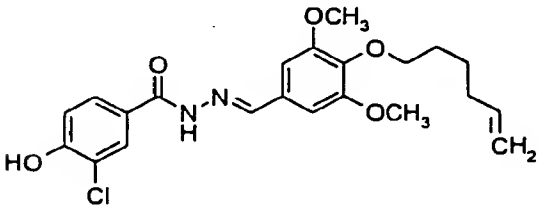
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-isopropylphenoxy) benzylid-ene]hydrazide



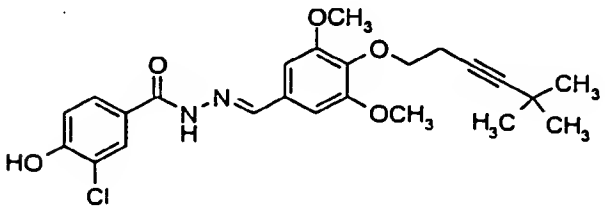
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethyl-2-pyridylmethoxy)- benzylidene]hydrazide



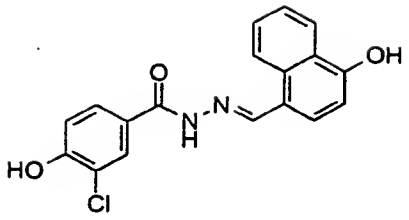
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(6-methylheptyloxy) benzylid-ene]hydrazide



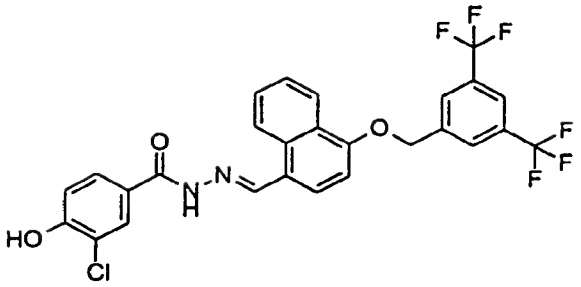
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(5-hexenyloxy) benzylid-ene]hydrazide



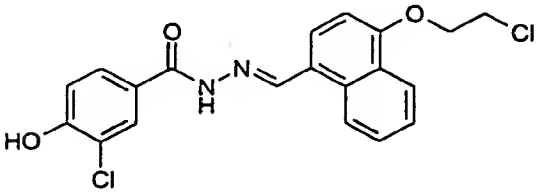
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(5,5-dimethyl-3-hexynyloxy) benzylidene]hydrazide



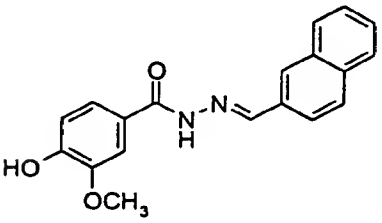
3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



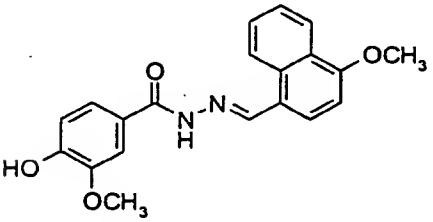
3-chloro-4-hydroxybenzoic acid [4-(3,5-bis-trifluoromethylbenzyloxy)-1-naphthylmethylene]hydrazide



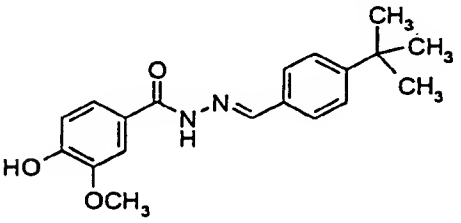
3-chloro-4-hydroxybenzoic acid [4-(2-chloroethoxy)-1-naphthylmethylene]hydrazide



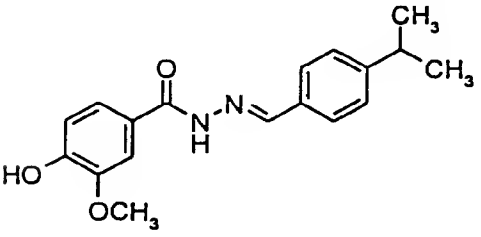
4-Hydroxy-3-methoxybenzoic acid (2-naphthylmethylene)hydrazide



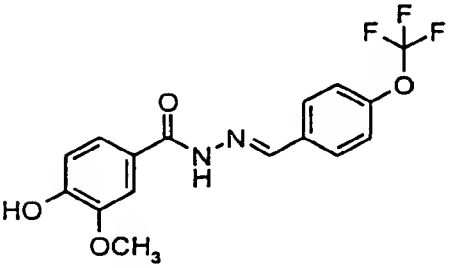
4-Hydroxy-3-methoxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide



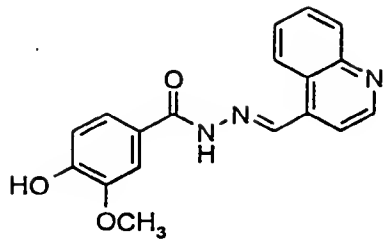
4-Hydroxy-3-methoxybenzoic acid (4-tert-butylbenzylidene)hydrazide



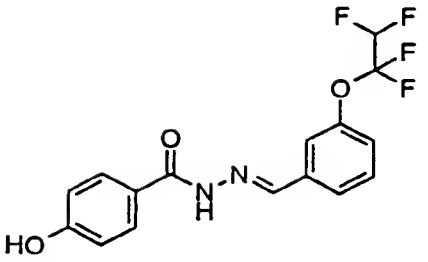
4-Hydroxy-3-methoxybenzoic acid (4-isopropylbenzylidene)hydrazide



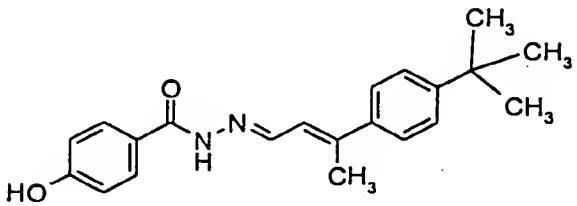
4-Hydroxy-3-methoxybenzoic acid (4-trifluoromethoxybenzylidene)hydrazide



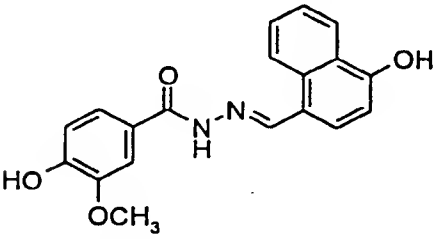
4-Hydroxy-3-methoxybenzoic acid (4-quinolinylmethylene)hydrazide



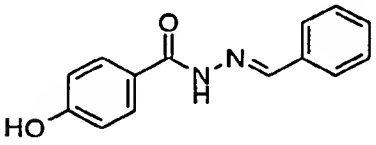
4-Hydroxybenzoic acid [3-(1,1,2,2-tetrafluoroethoxy)benzylidene]hydrazide



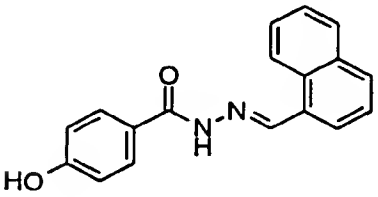
4-Hydroxybenzoic acid [3-(4-tert-butylphenyl)-E-but-2-enylidene]hydrazide



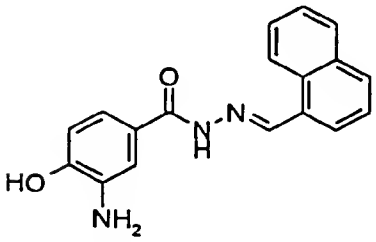
4-Hydroxy-3-methoxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



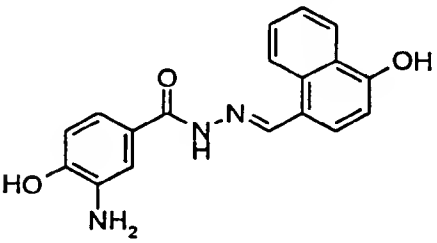
4-Hydroxybenzoic acid (benzylidene)hydrazide



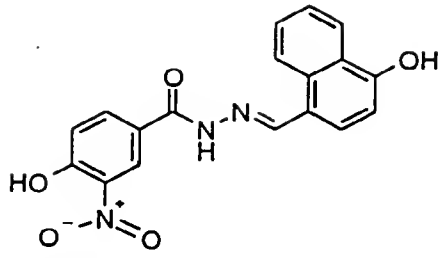
4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide



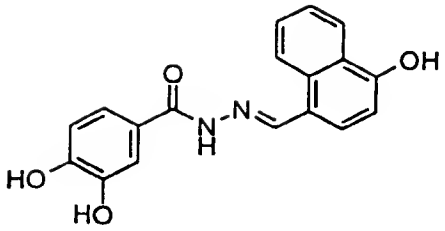
3-Amino-4-hydroxybenzoic acid (1- naphthyl-methylene)hydrazide



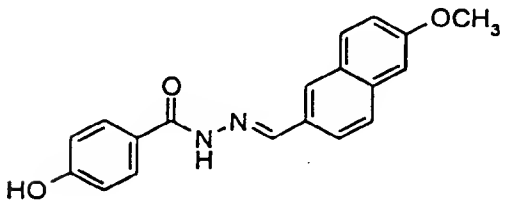
3-Amino-4-hydroxybenzoic acid (4-hydroxy-1- naphthylmethylene)hydrazide



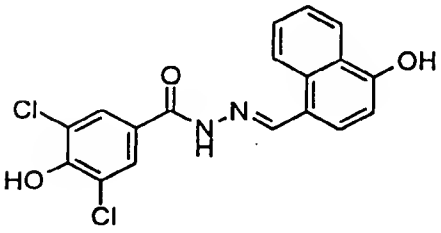
4-Hydroxy-3-nitrobenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



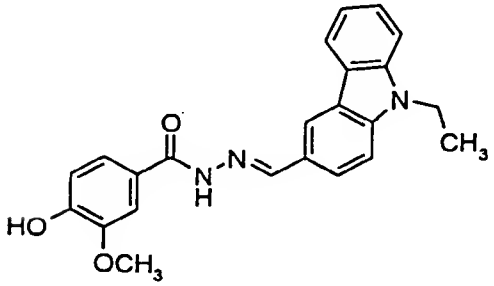
3,4-Dihydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



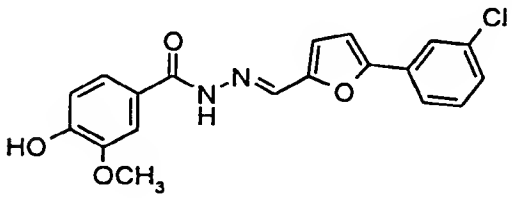
4-Hydroxybenzoic acid (6-methoxy-2-naphthylmethylene)hydrazide



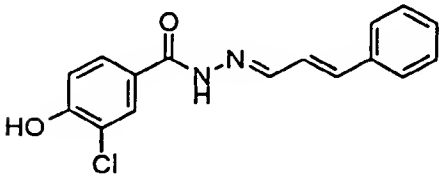
3,5-Dichloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



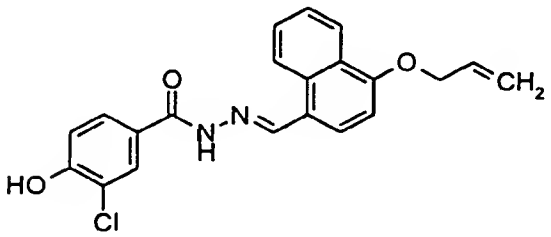
4-Hydroxy-3-methoxybenzoic acid (9-ethyl-9H-3-carbazolylmethylene)hydrazide



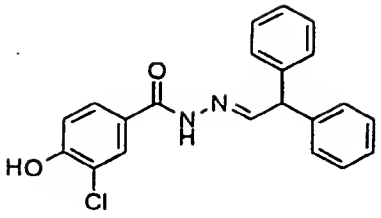
4-Hydroxy-3-methoxybenzoic acid [5-(3-chlorophenyl)-2-furanylmethylene]hydrazide



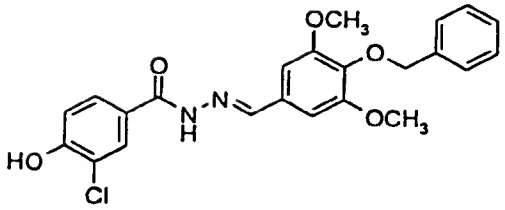
3-Chloro-4-hydroxybenzoic acid (3-phenyl-E-allylidene)hydrazide



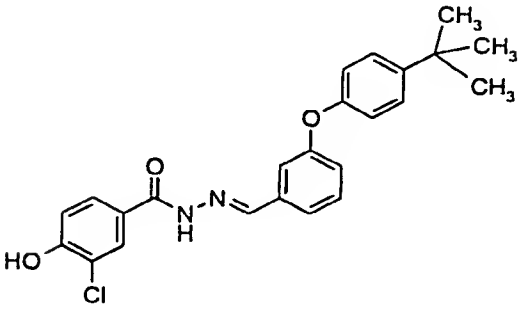
3-Chloro-4-hydroxybenzoic acid (4-allyloxy-1-naphtylmethylene)hydrazide



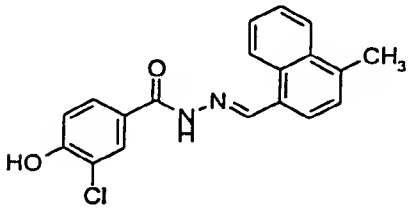
3-Chloro-4-hydroxybenzoic acid (2,2-diphenylethylidene)hydrazide



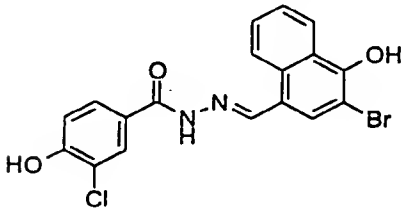
3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-3,5-dimethoxybenzylidene)hydrazide



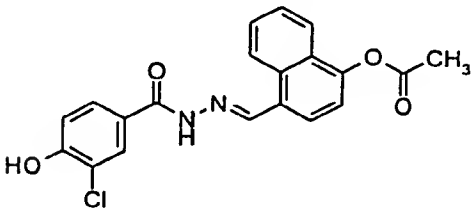
3-Chloro-4-hydroxybenzoic acid [3-(4-tert-butylphenoxy)benzylidene]hydrazide



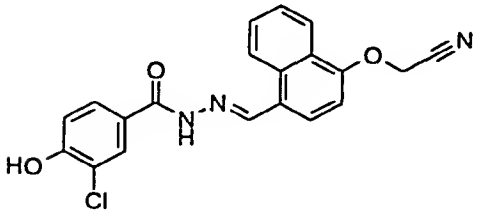
3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide



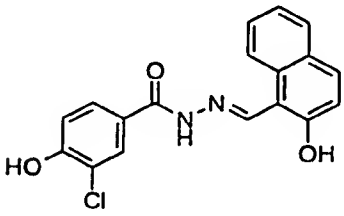
3-Chloro-4-hydroxybenzoic acid (3-bromo-4-hydroxy-1-naphthylmethylene)hydrazide



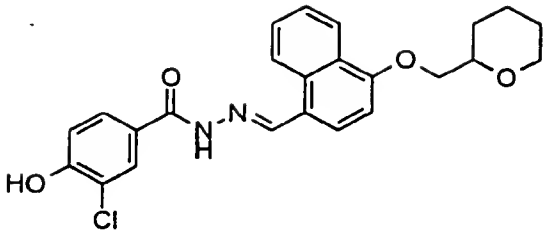
Acetic acid 4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester



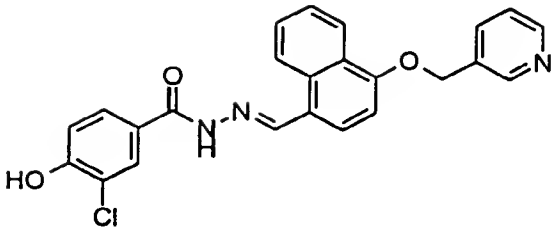
3-Chloro-4-hydroxybenzoic acid (4-cyanomethoxy-1-naphthylmethylene)hydrazide



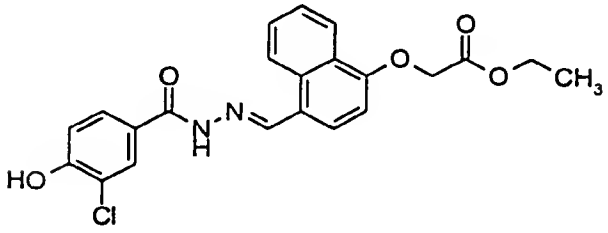
3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide



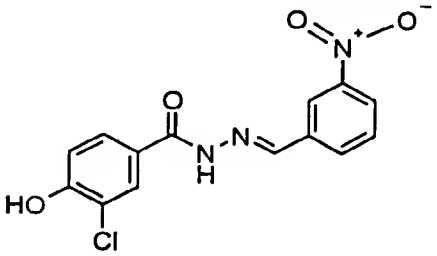
3-Chloro-4-hydroxybenzoic acid [4-(tetrahydro-2-pyranylmethoxy)-1-naphthyl-methylene]hydrazide



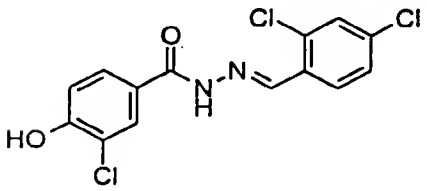
3-Chloro-4-hydroxybenzoic acid [4-(3-pyridylmethoxy)-1-naphthylmethylene]hydrazide



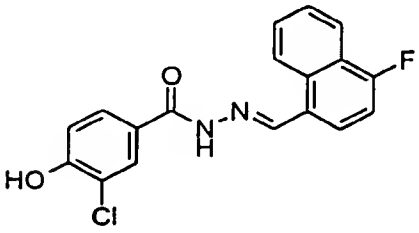
4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxy)acetic acid ethyl ester



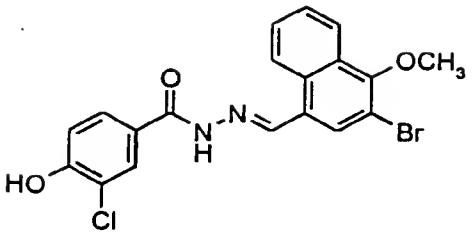
3-Chloro-4-hydroxybenzoic acid (3-nitrobenzylidene)hydrazide



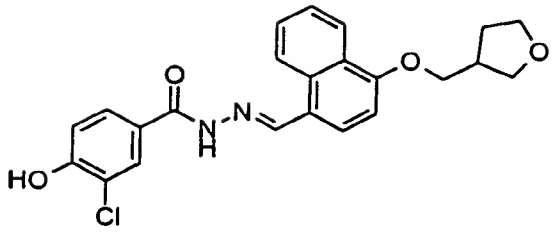
3-Chloro-4-hydroxybenzoic acid (2,4-dichlorobenzylidene)hydrazide



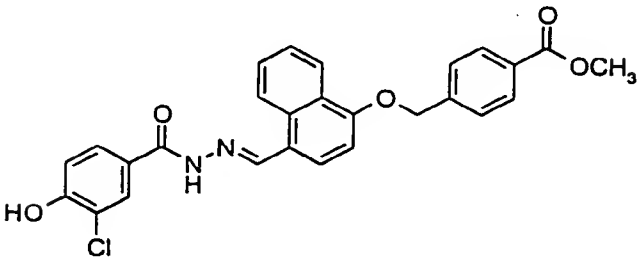
3-Chloro-4-hydroxybenzoic acid (4-fluoro-1-naphthylmethylene)hydrazide



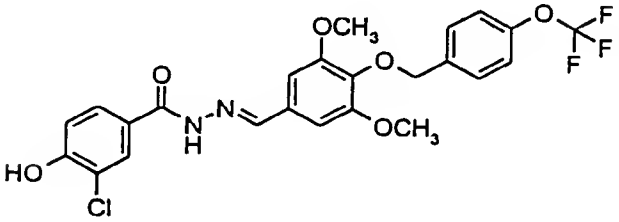
3-Chloro-4-hydroxybenzoic acid (3-bromo-4-methoxy-1-naphthylmethylene)hydrazide



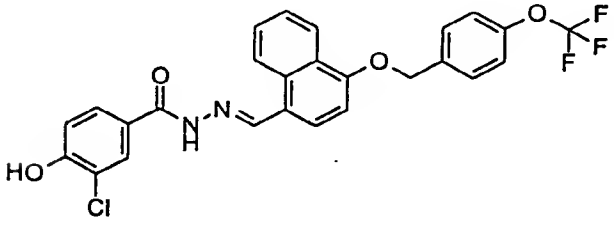
3-Chloro-4-hydroxybenzoic acid [4-(3-tetrahydrofuranylmethoxy)-1-naphthylmethylene]hydrazide



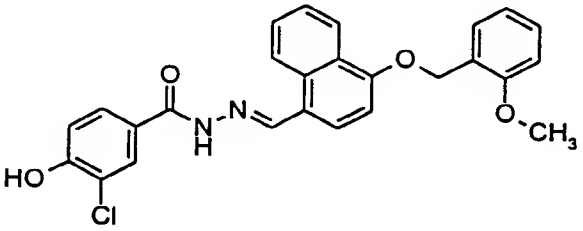
4-(4-[3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxymethyl)benzoic acid methyl ester



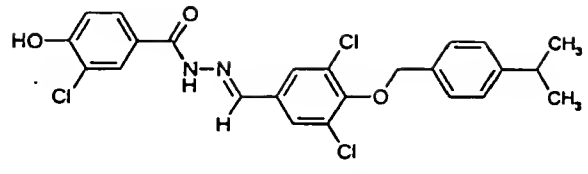
3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethoxybenzyloxy)-benzylidene]hydrazide

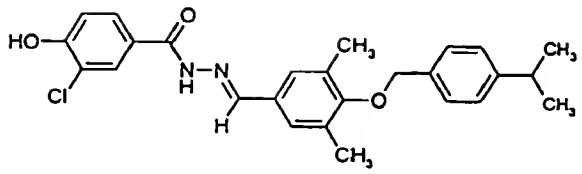


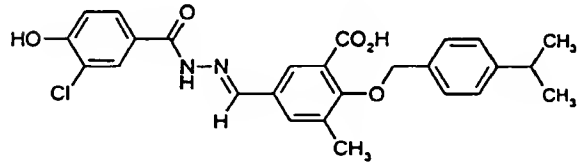
3-Chloro-4-hydroxybenzoic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]hydrazide

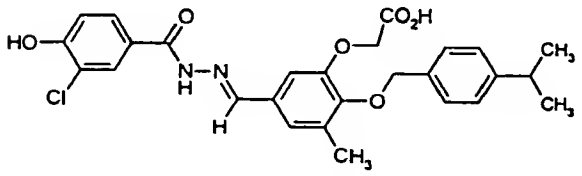


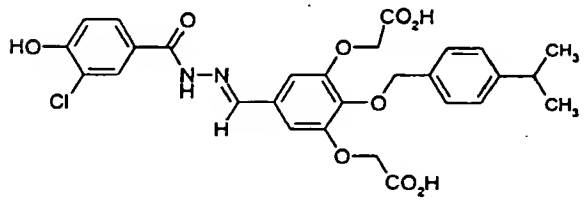
3-Chloro-4-hydroxybenzoic acid [4-(2-methoxybenzyloxy)-1-naphthylmethylene]hydrazide

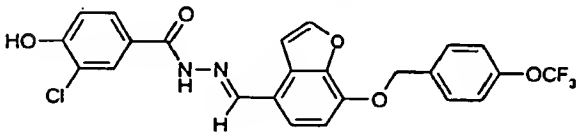


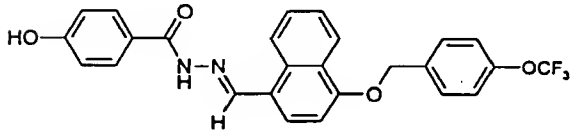


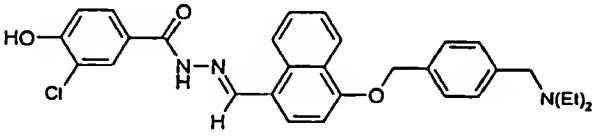


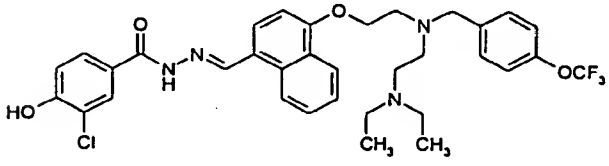


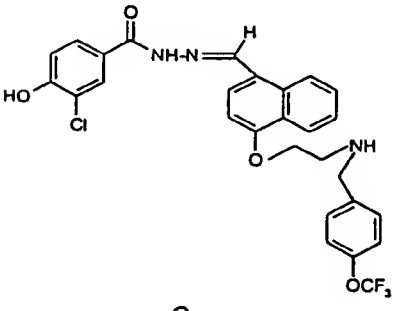


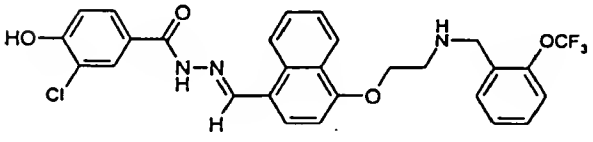


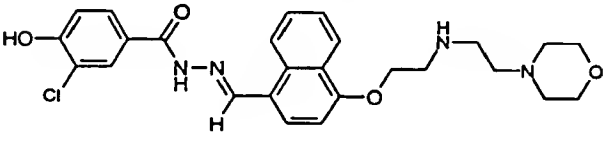


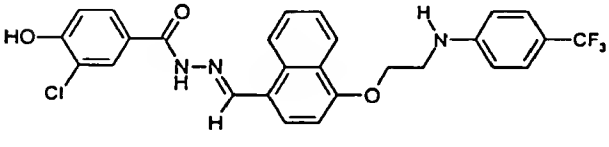


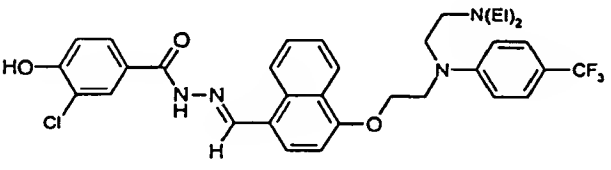


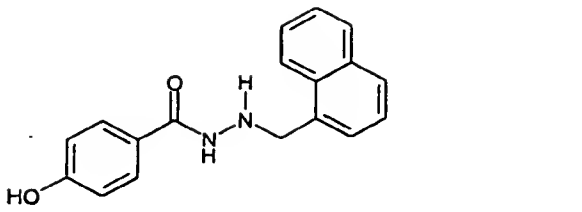
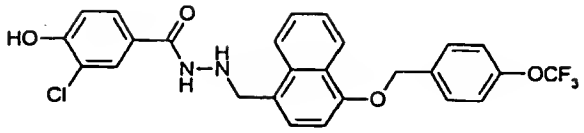
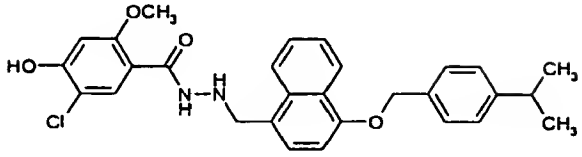
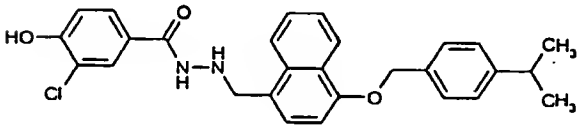
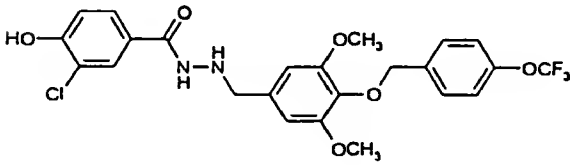
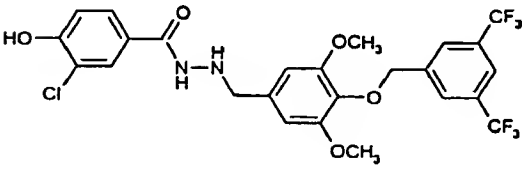
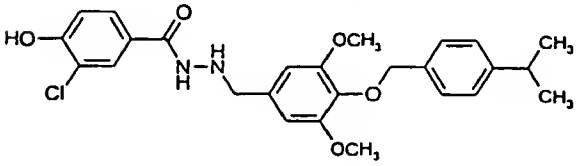




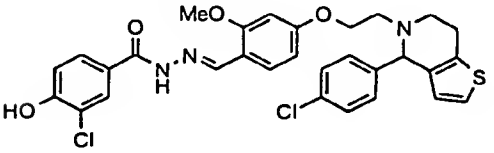
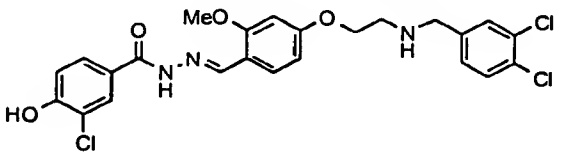
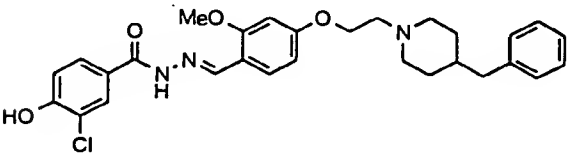
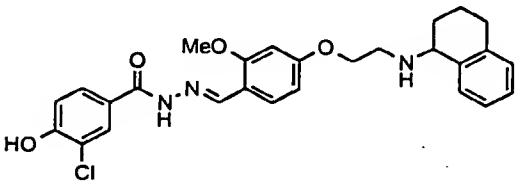
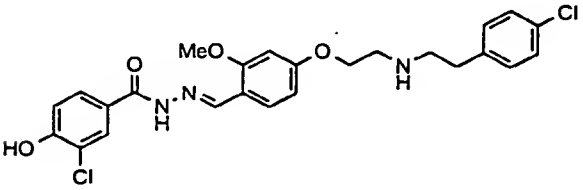
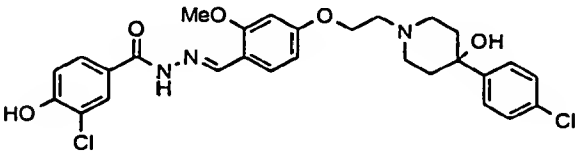
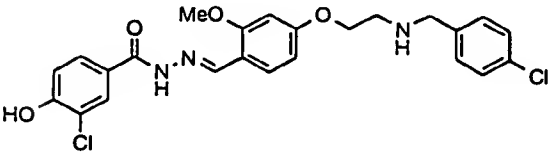
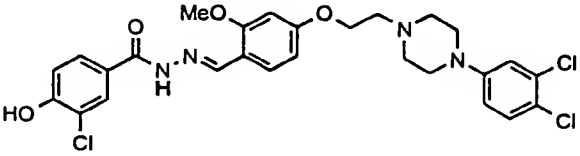
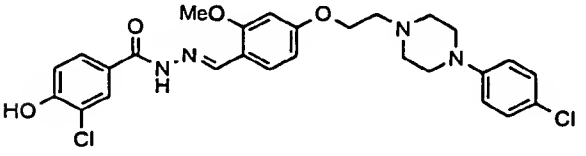
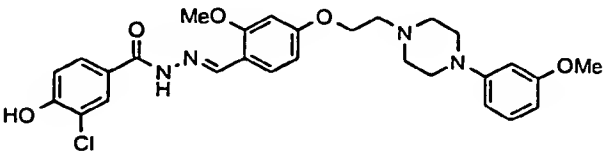


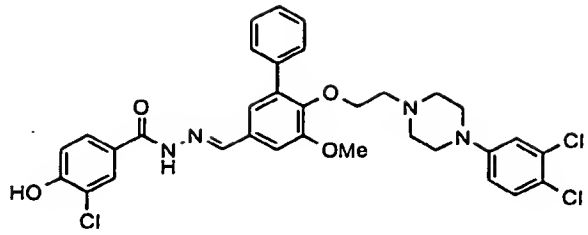


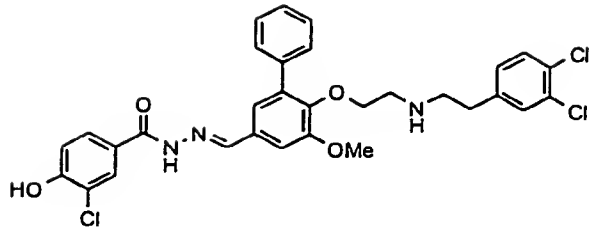


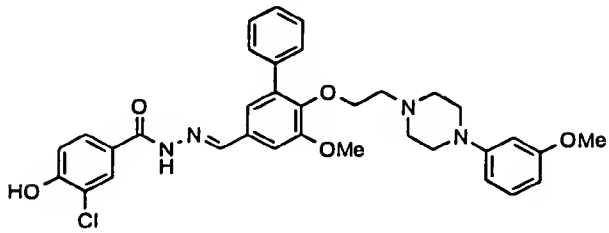








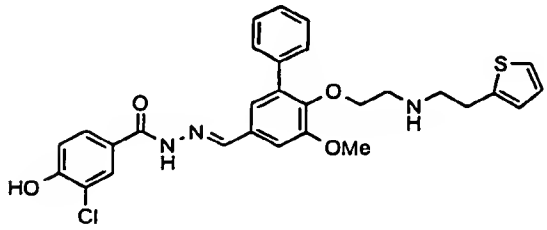
Preferred specific compounds represented by the formulae VI and VII are the following:

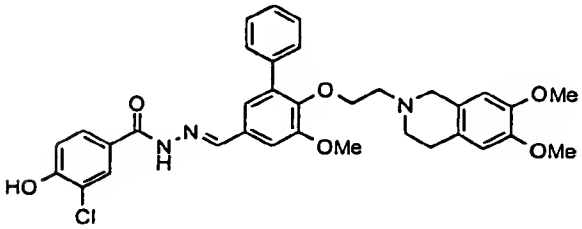











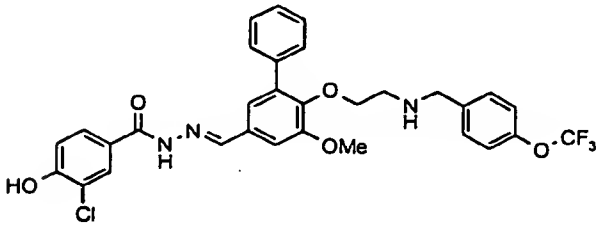


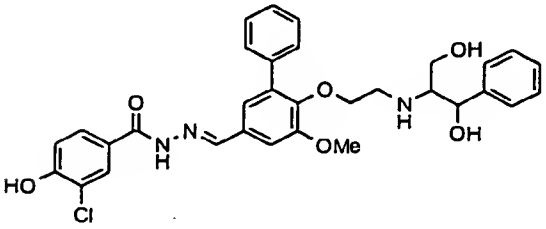


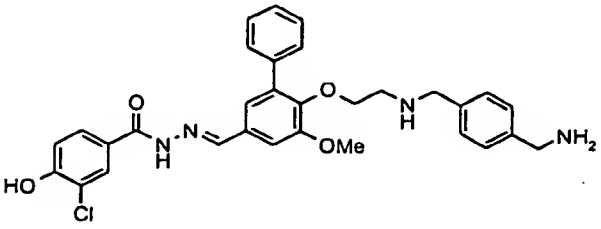


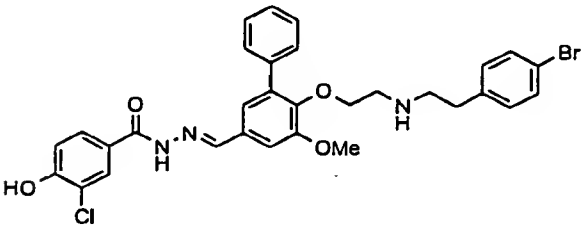


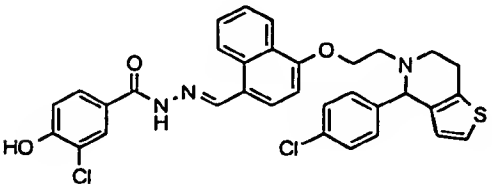


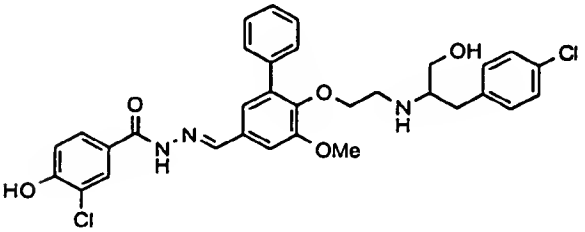


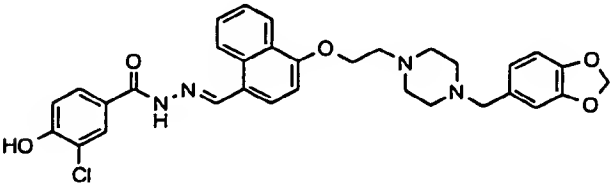


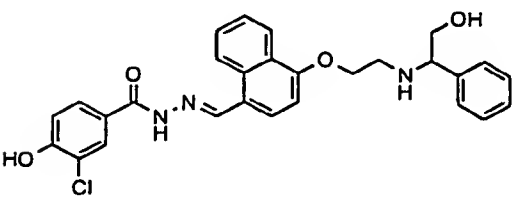


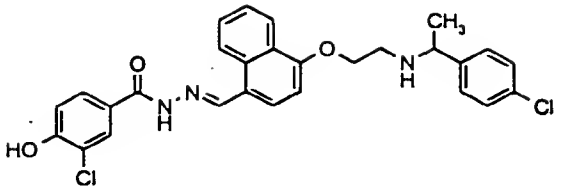


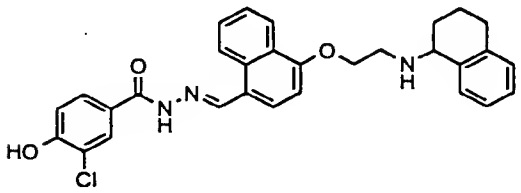


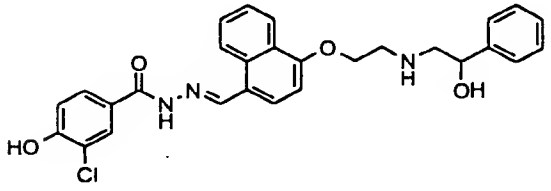


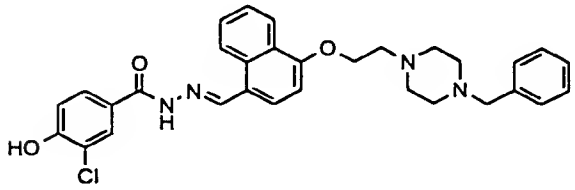


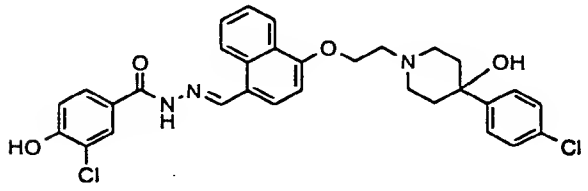


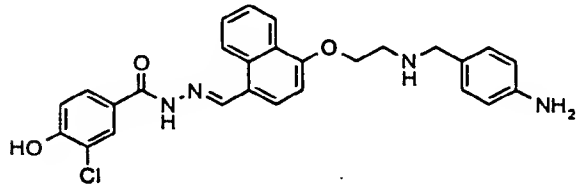


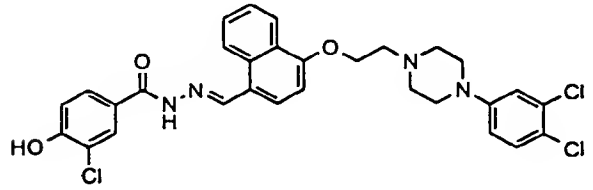


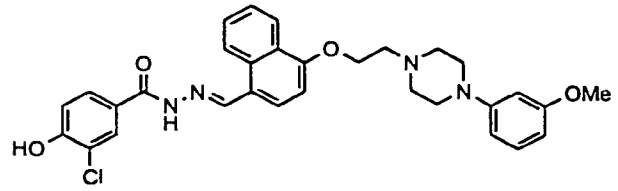


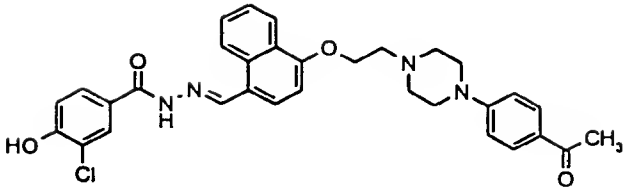


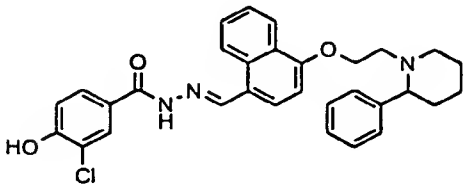


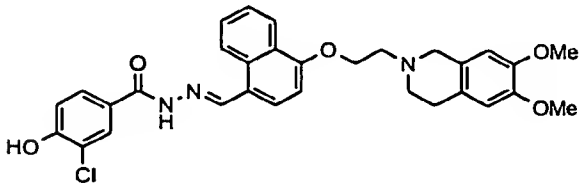


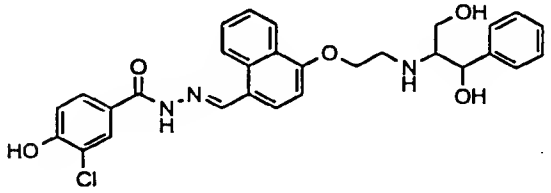


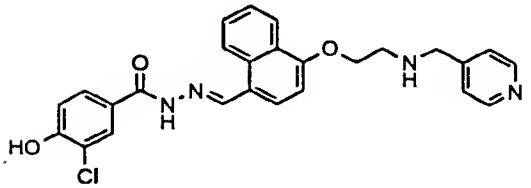


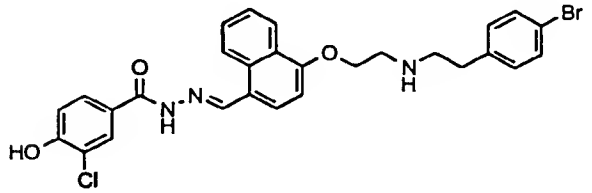


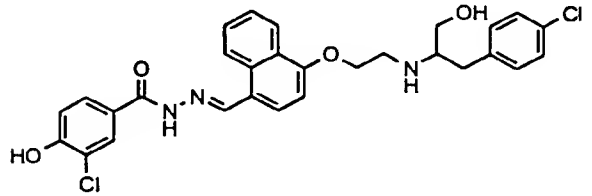


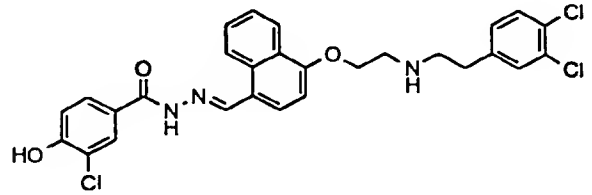


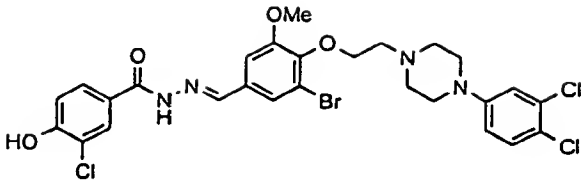


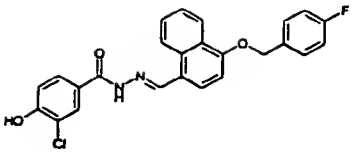


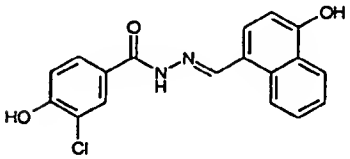


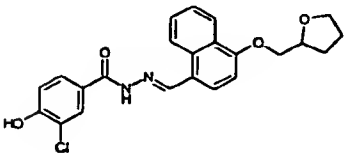


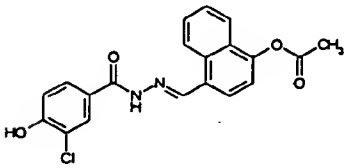


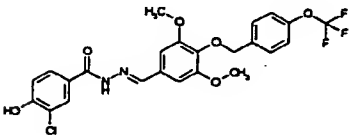


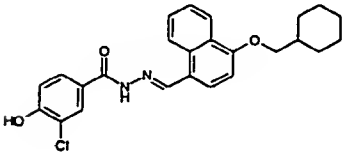


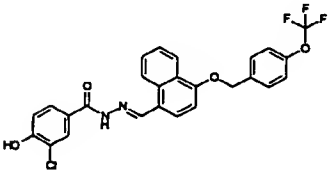


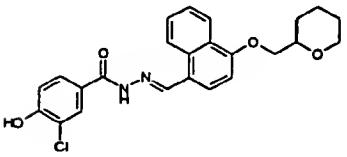


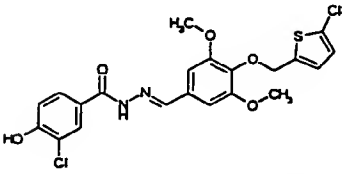


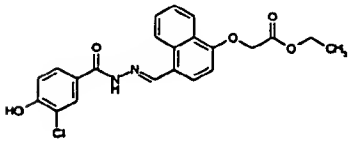


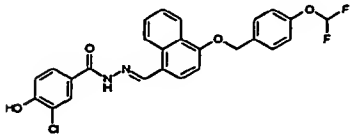


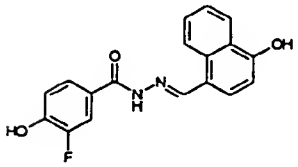


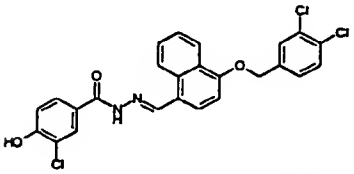


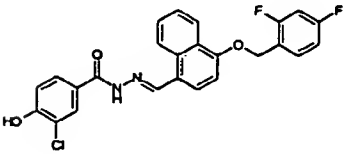


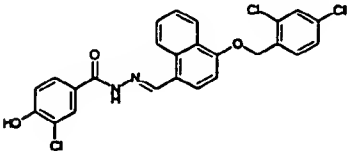


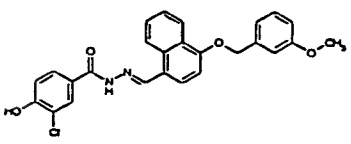


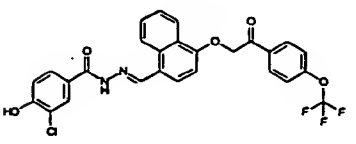


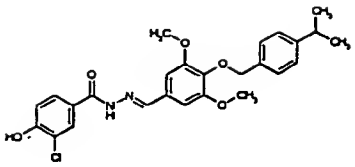


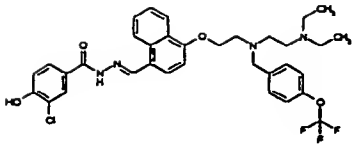


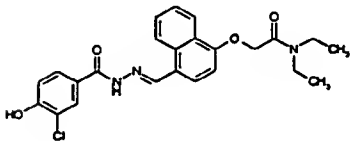


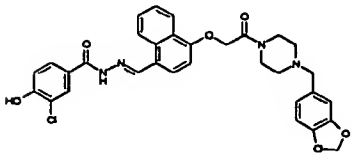


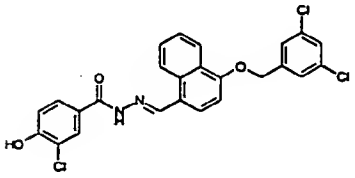


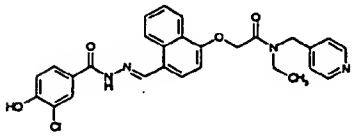


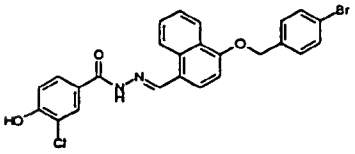


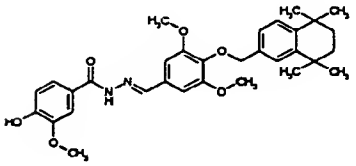


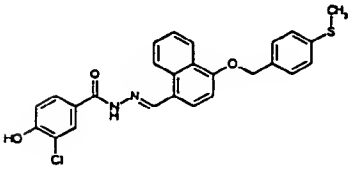


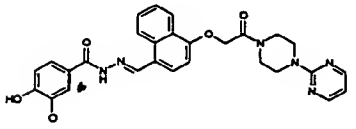


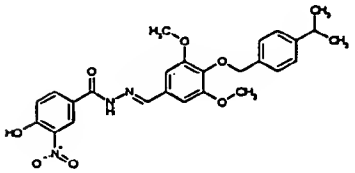


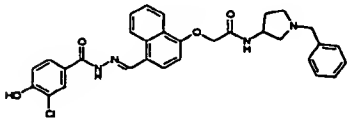


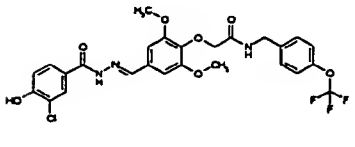


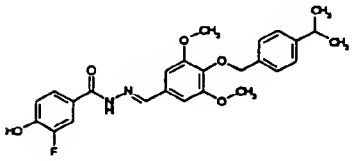


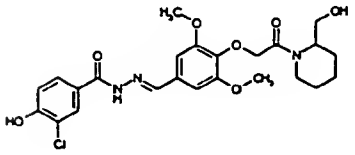


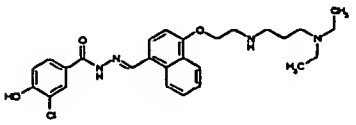


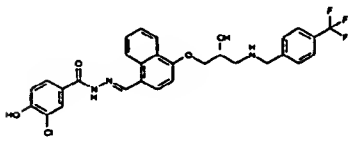


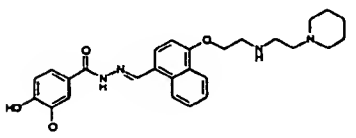


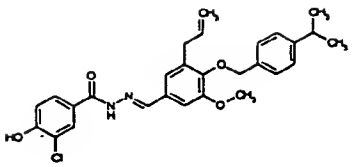


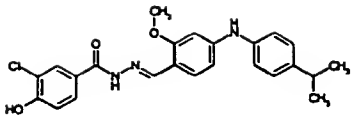


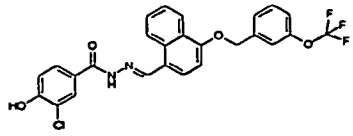


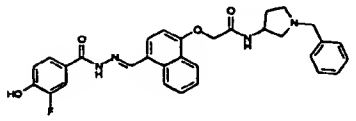


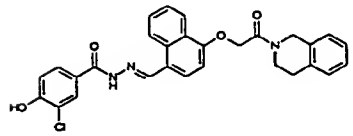


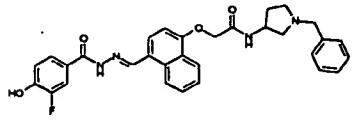


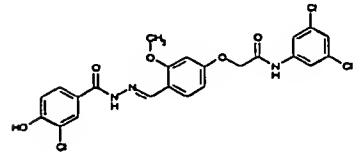


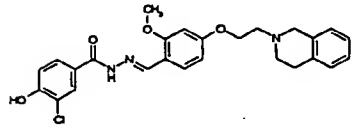


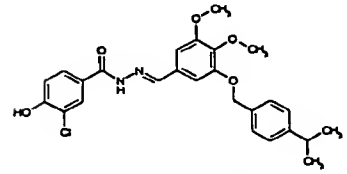


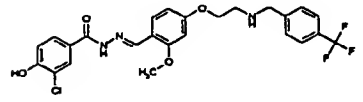


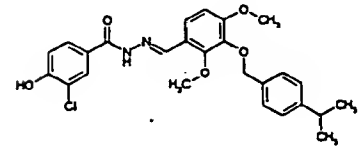


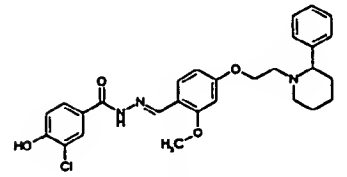


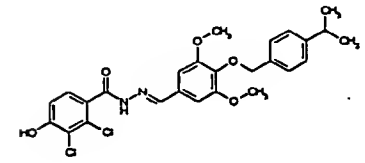


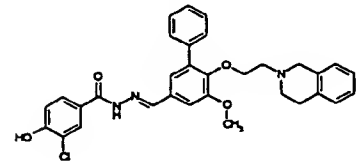


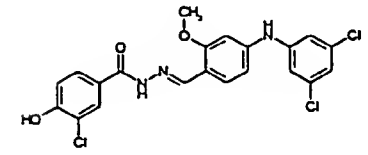


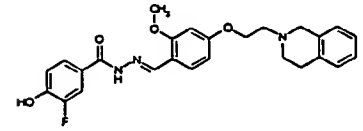


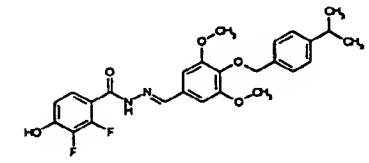


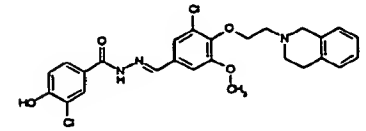


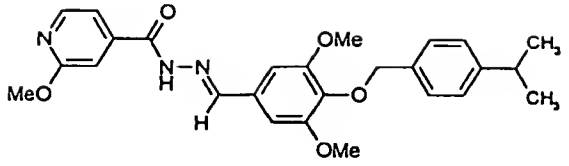


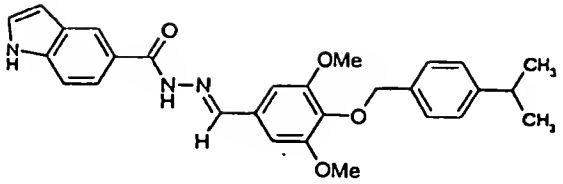


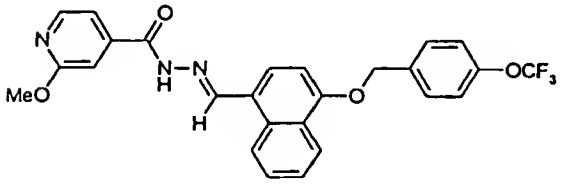


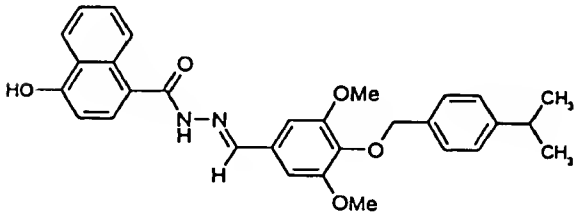


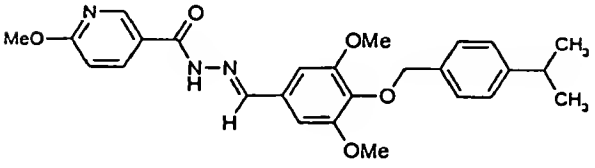


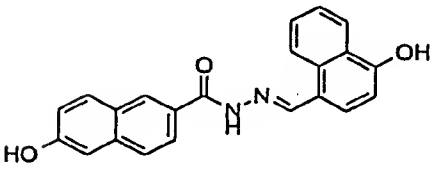


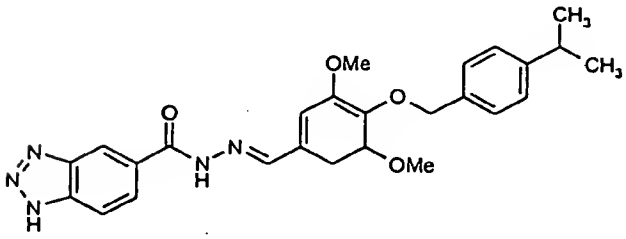


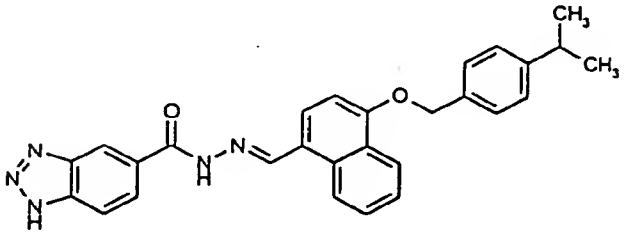


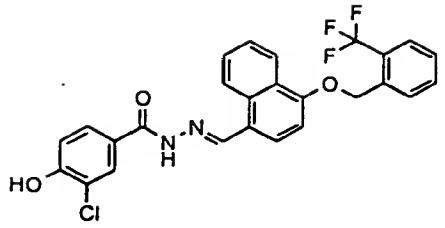


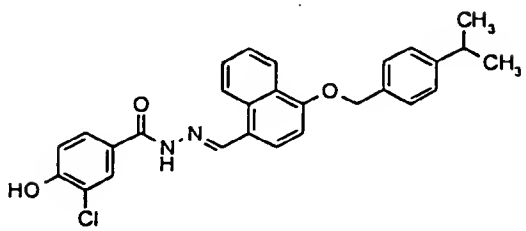


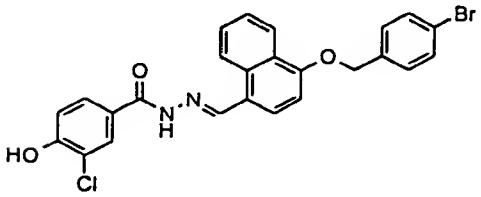


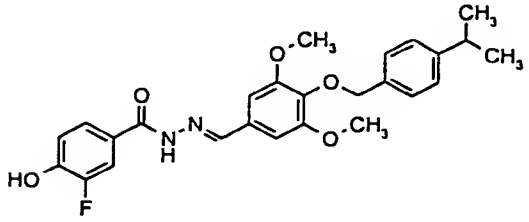


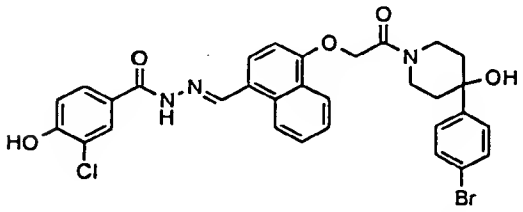


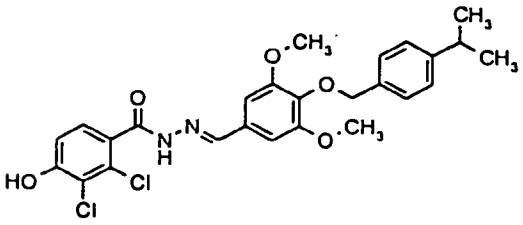


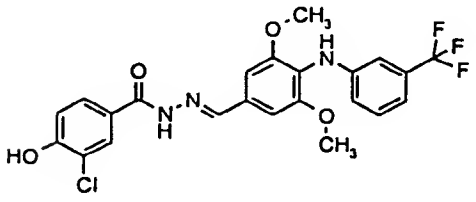


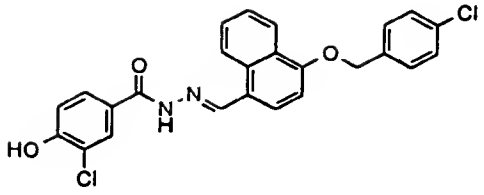


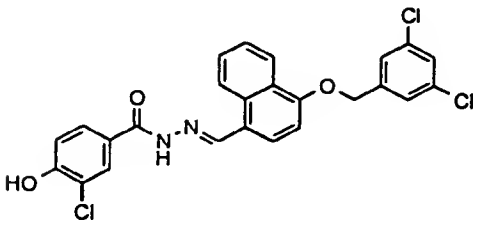


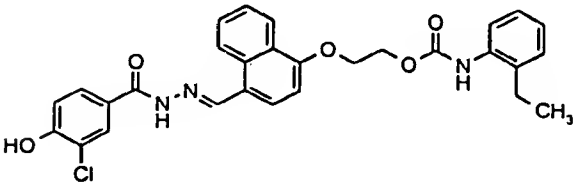


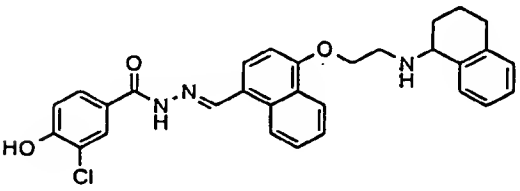


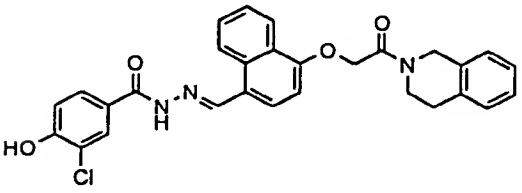


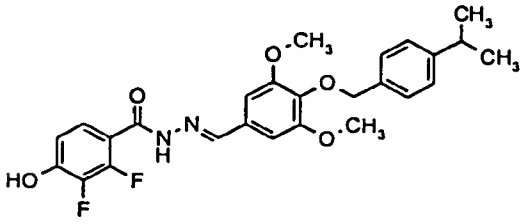


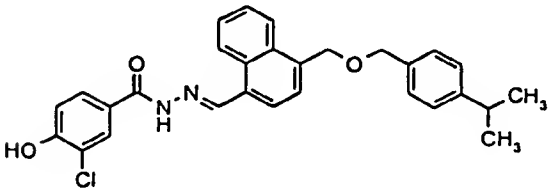


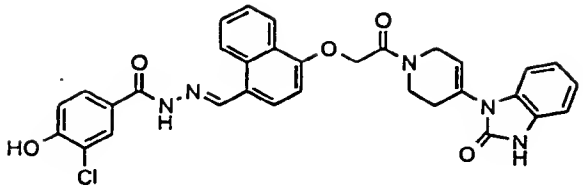


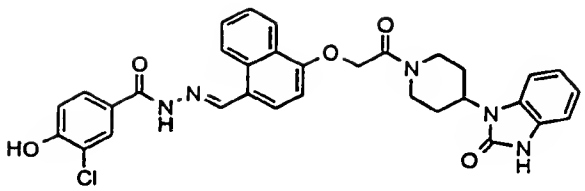


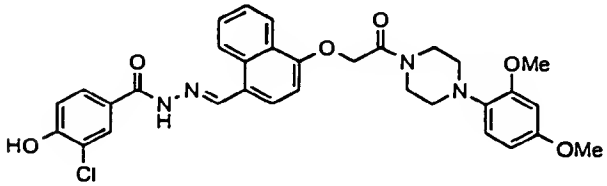


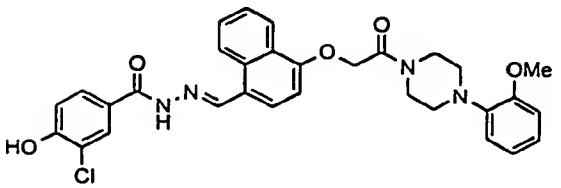


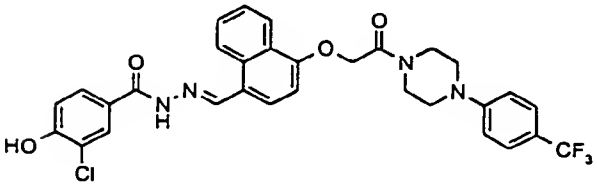


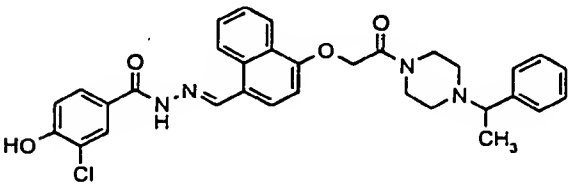


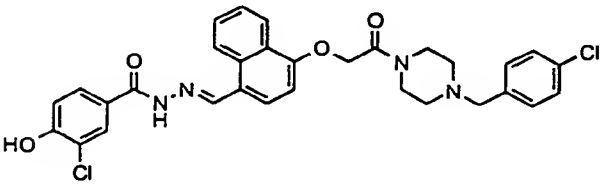


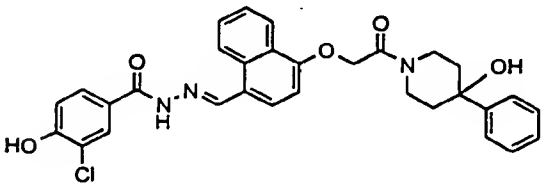


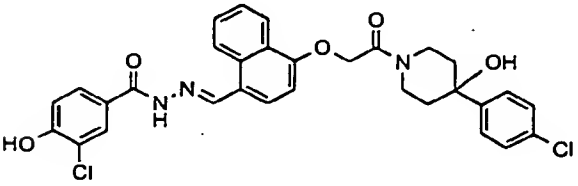


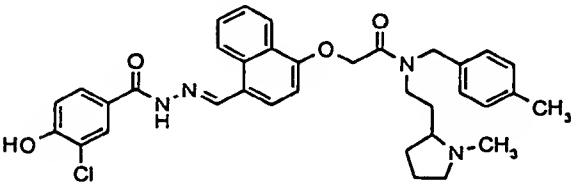


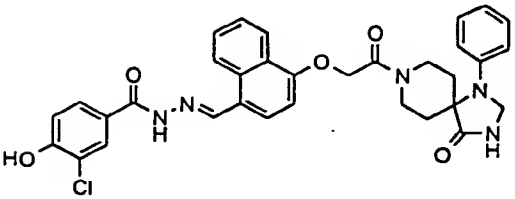


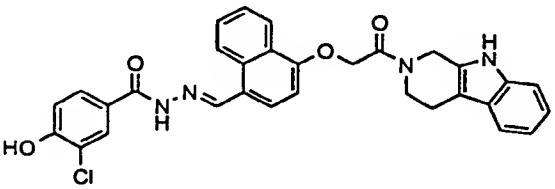


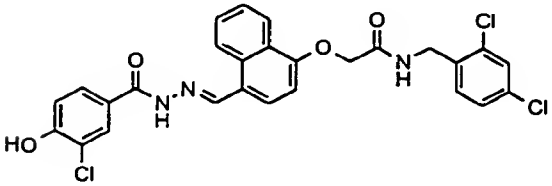


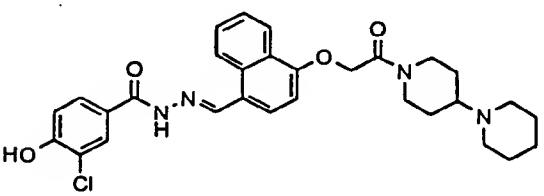


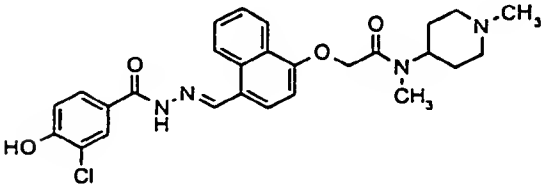


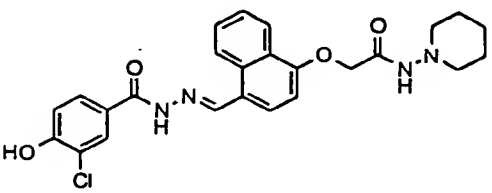


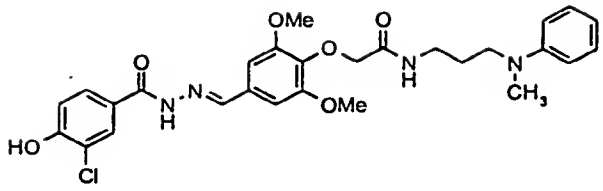


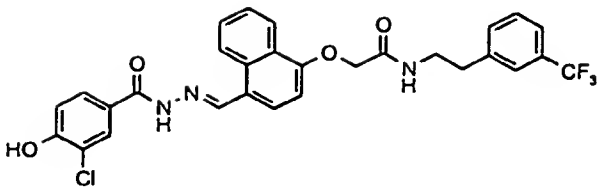


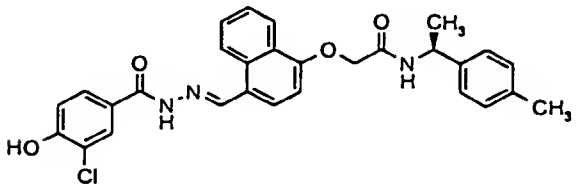


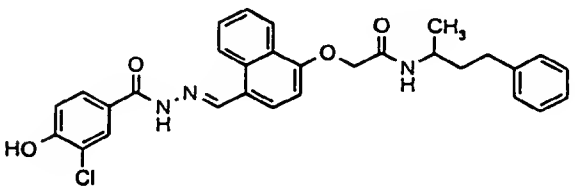


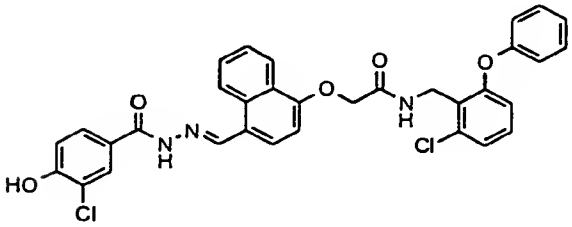


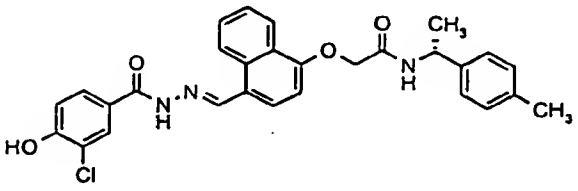


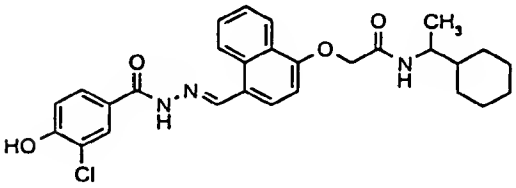


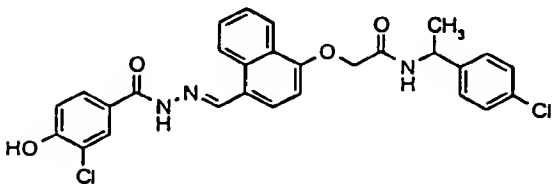


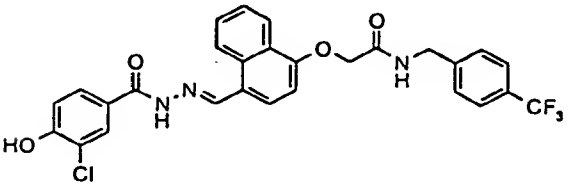


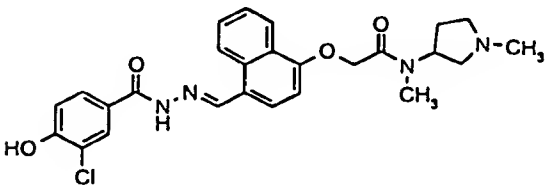


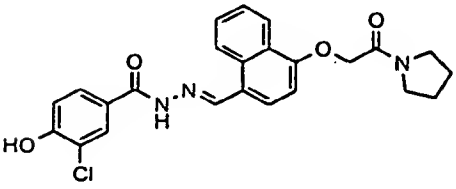


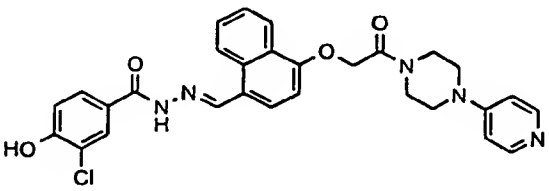


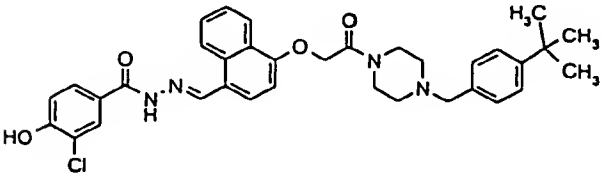


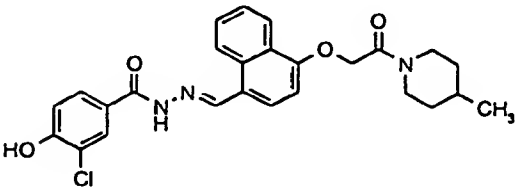


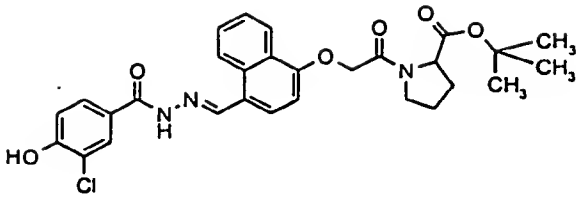


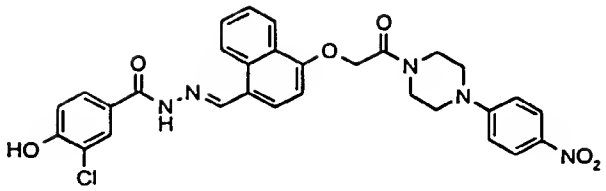


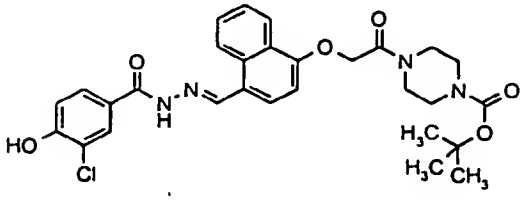


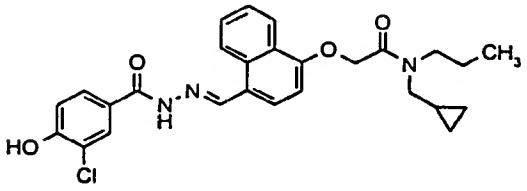


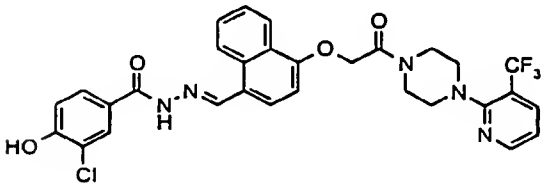


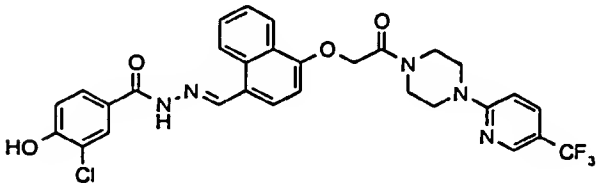


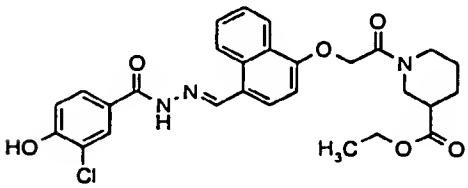


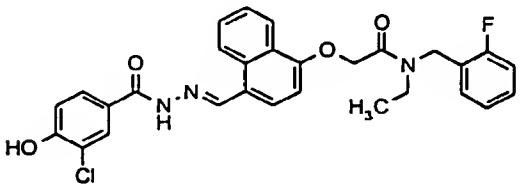


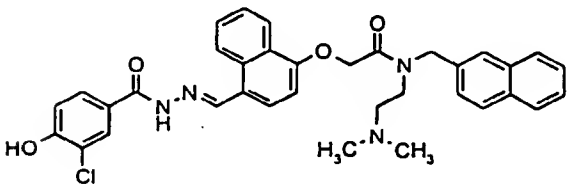


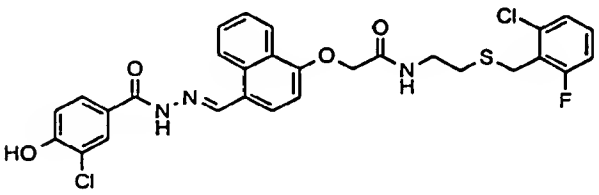


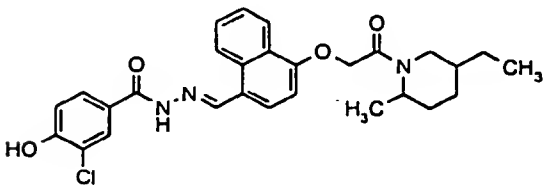


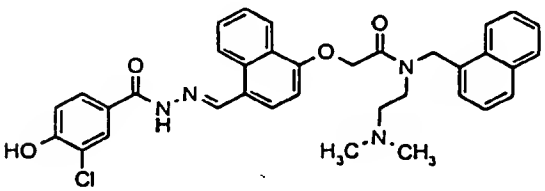


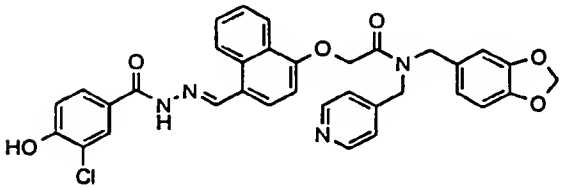


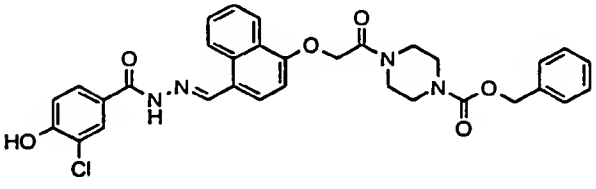


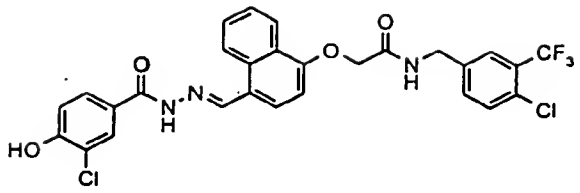


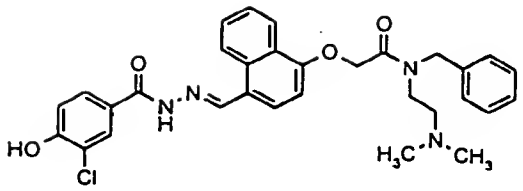


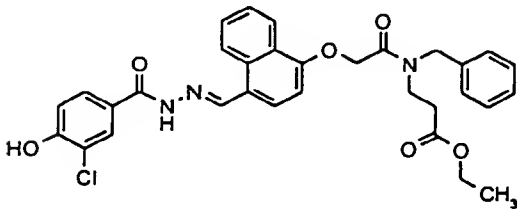


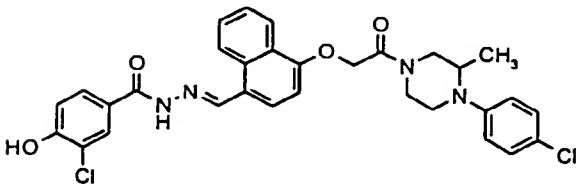


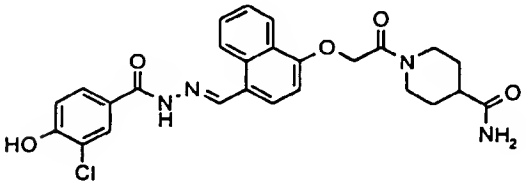


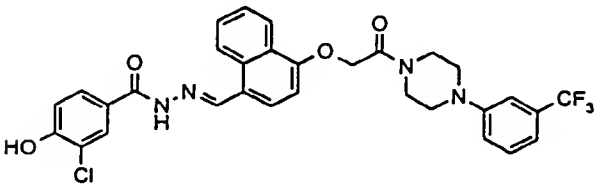


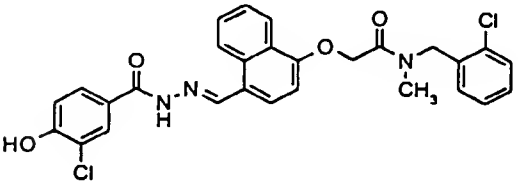


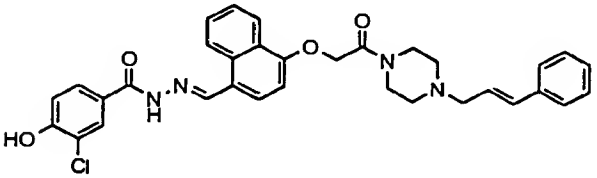


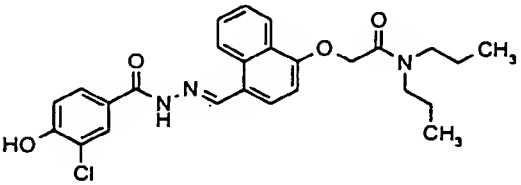


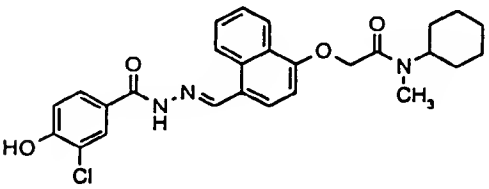


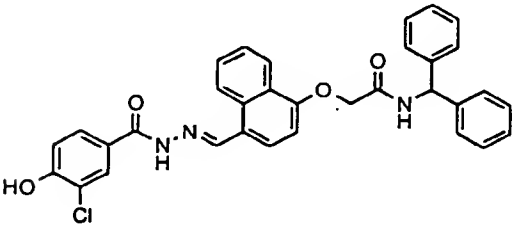


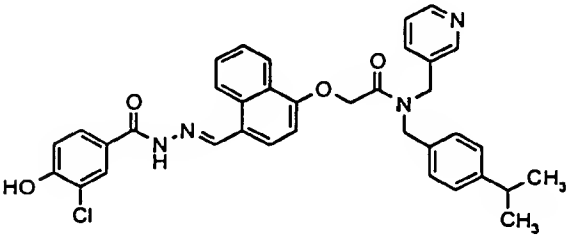


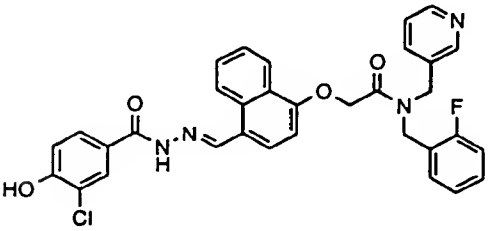


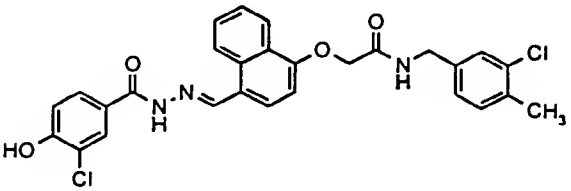


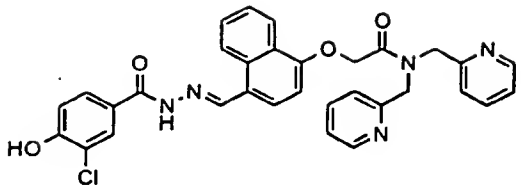


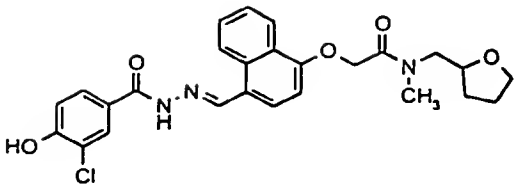


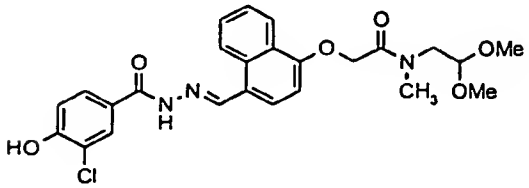


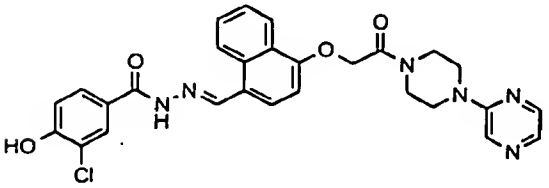


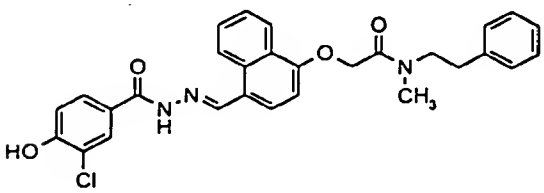


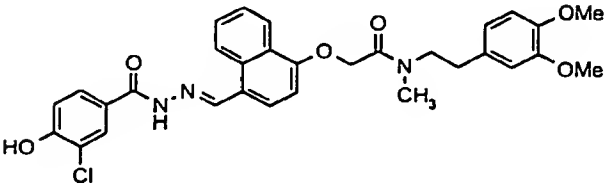


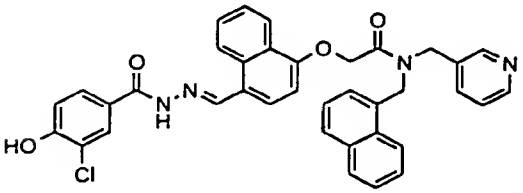


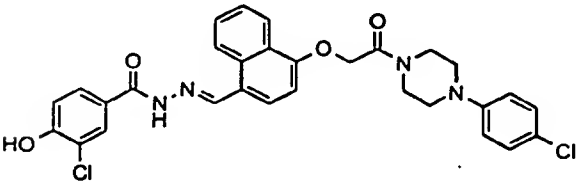


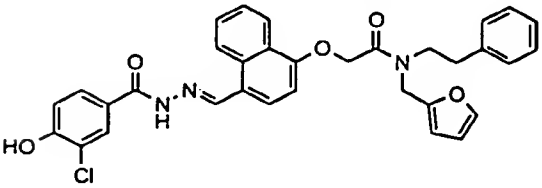


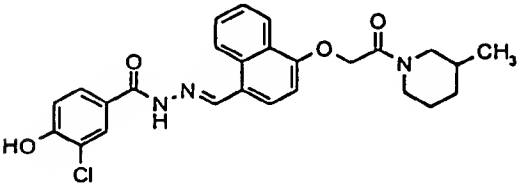


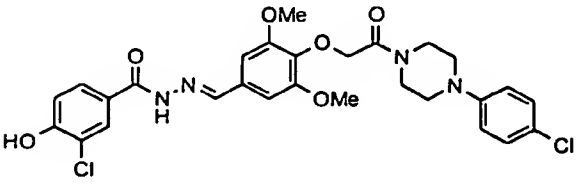


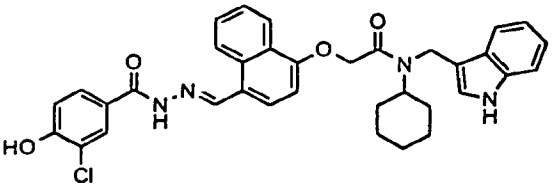


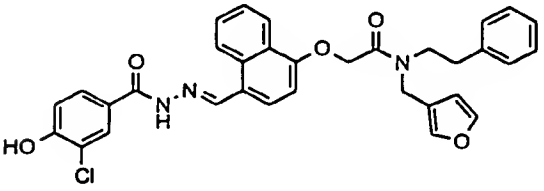


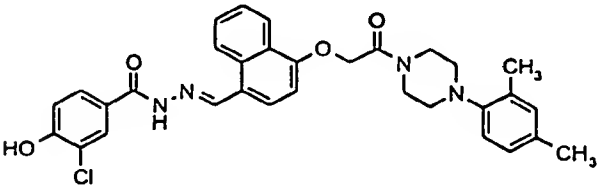


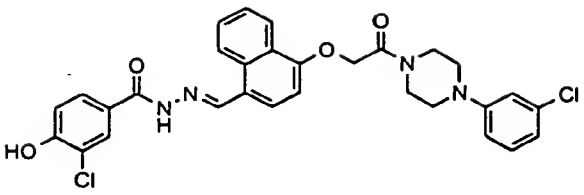


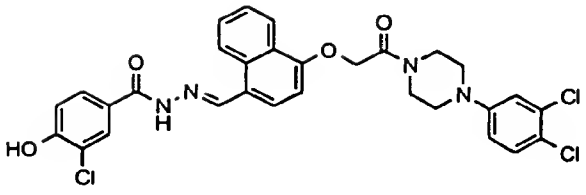


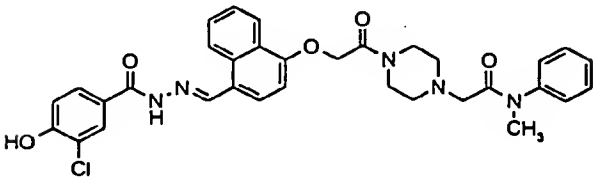


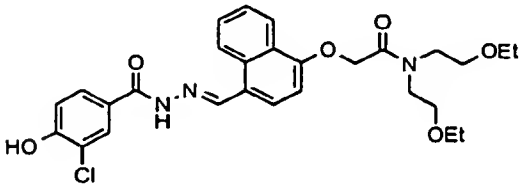


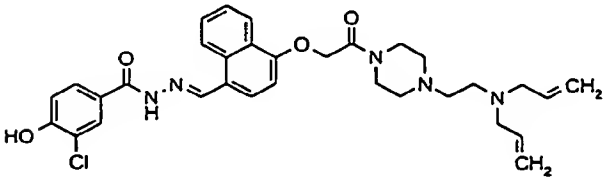


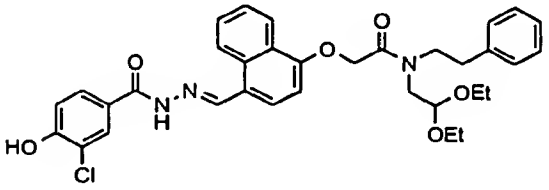


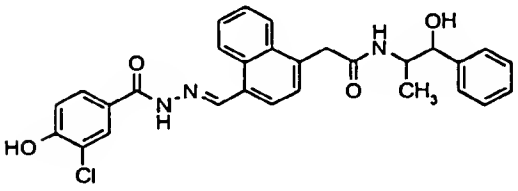


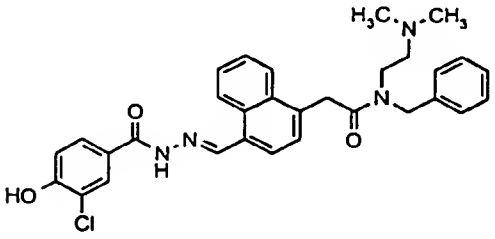


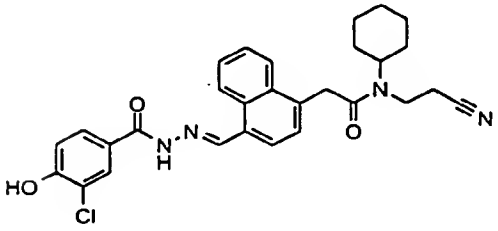


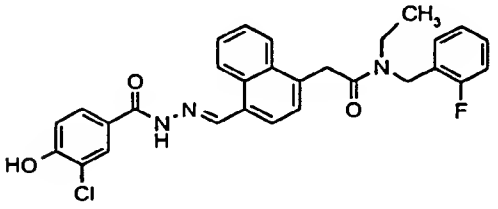


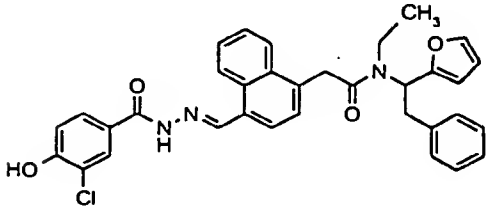


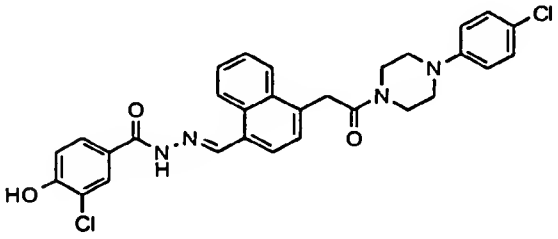


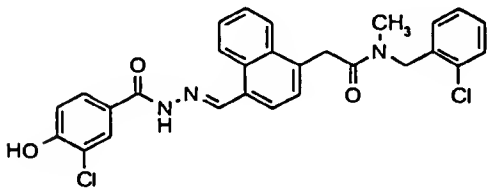


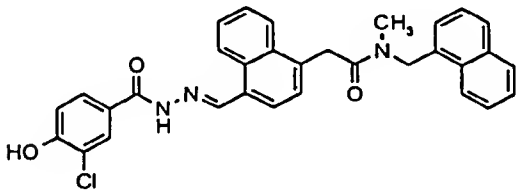


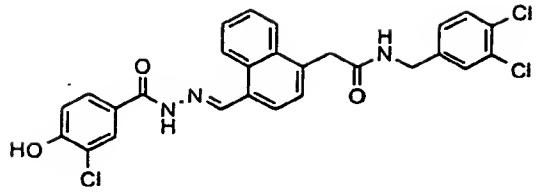


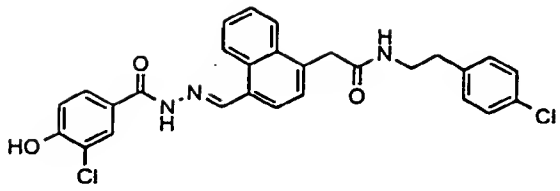


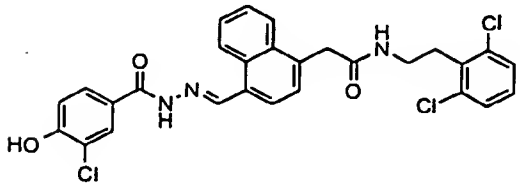


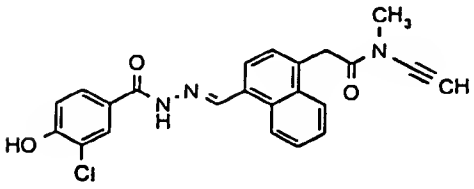


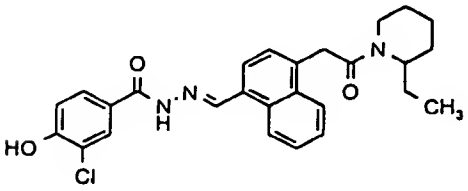


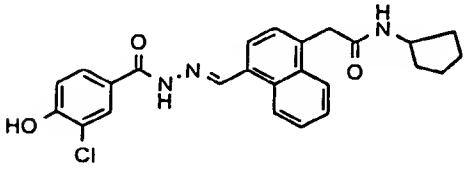


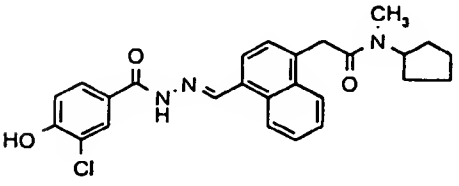


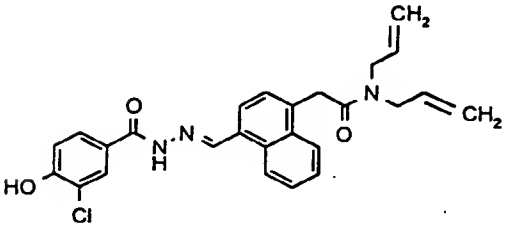


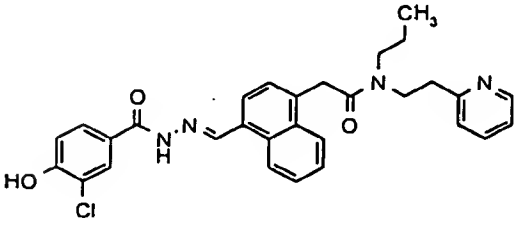


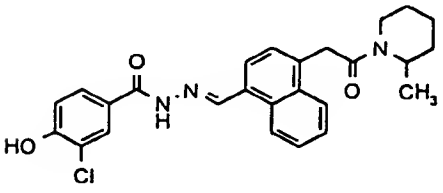


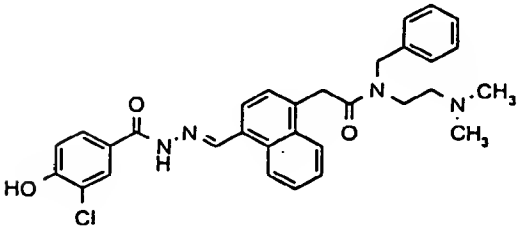


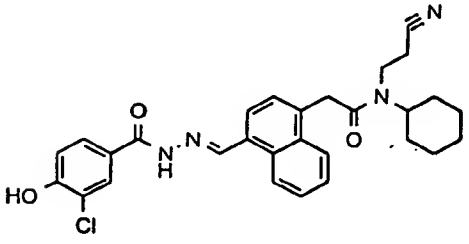


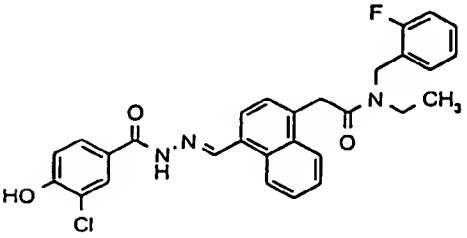


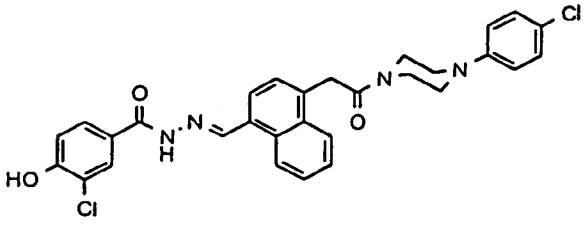


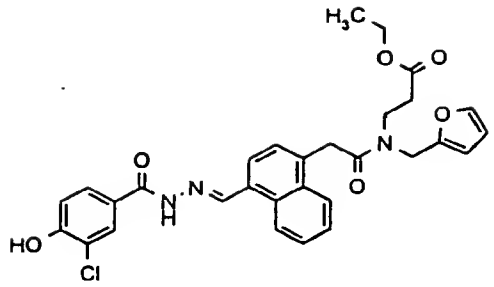


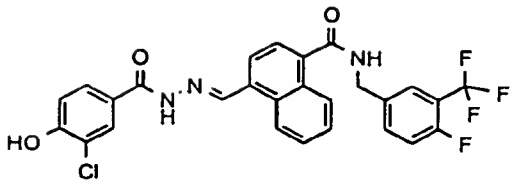


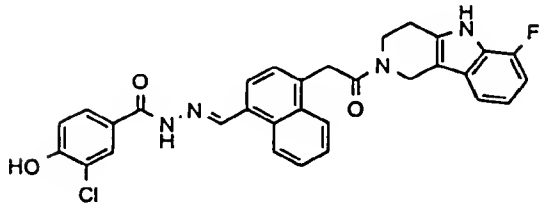


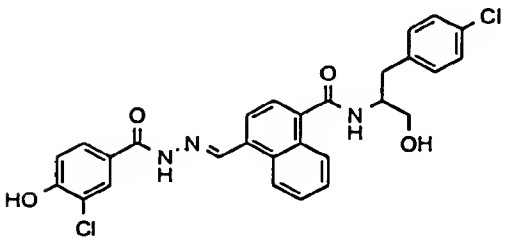


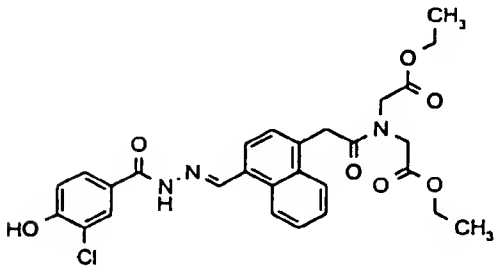


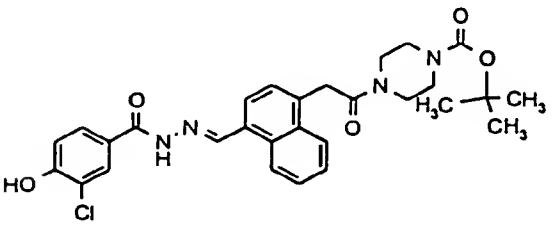


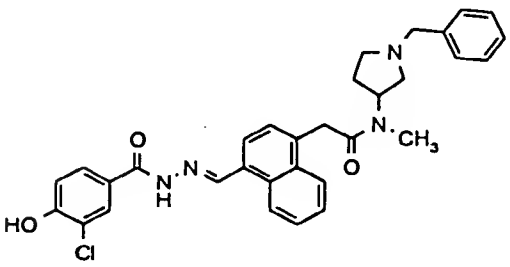


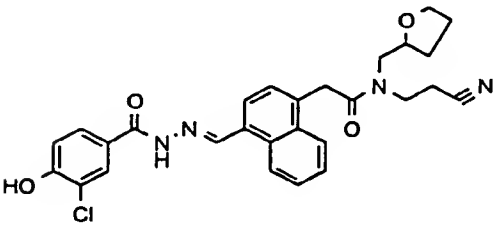


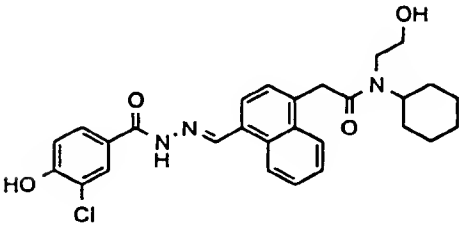


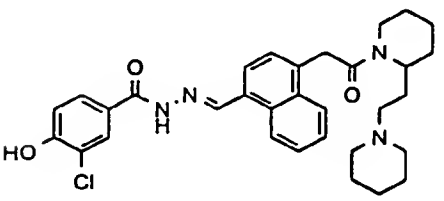


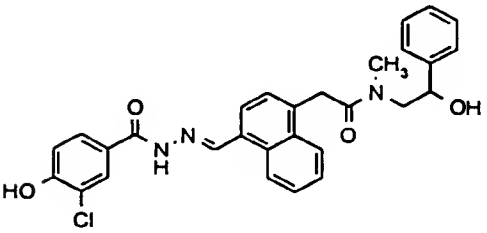


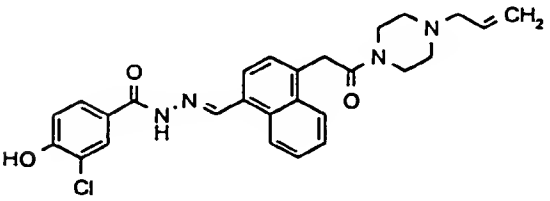


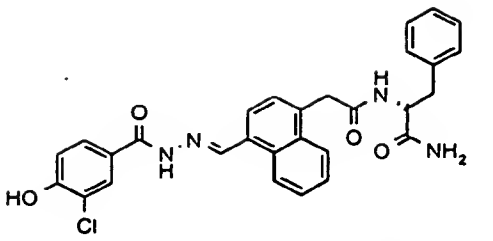


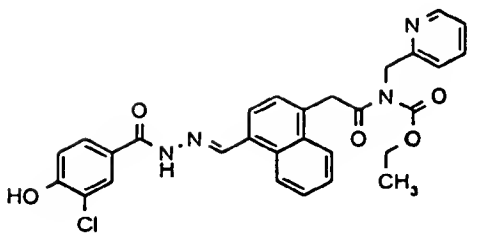


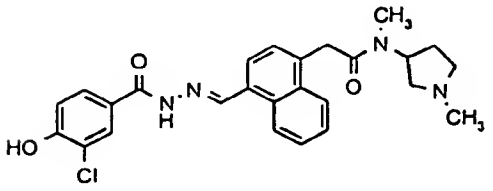


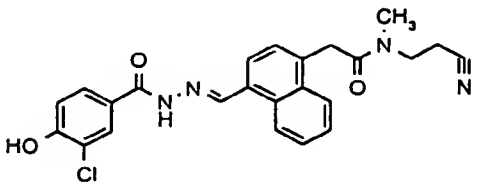


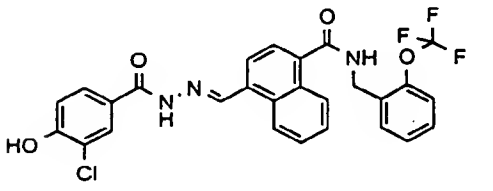


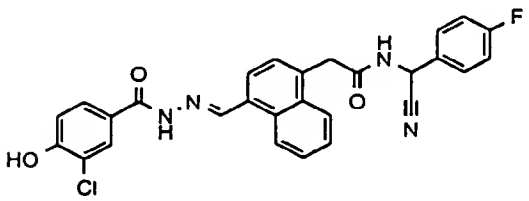


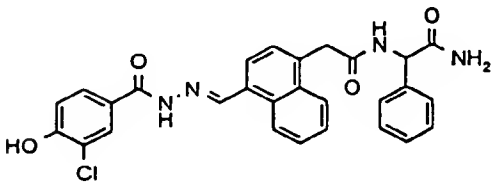


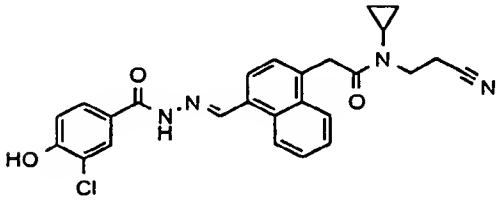


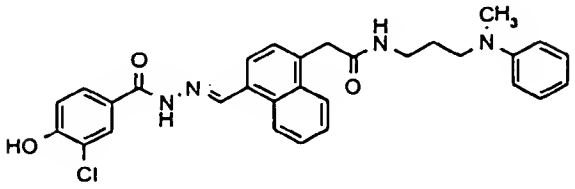


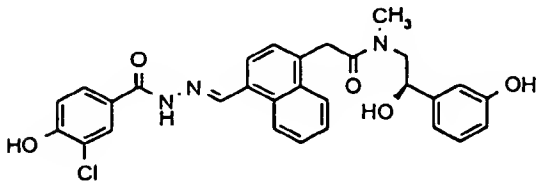


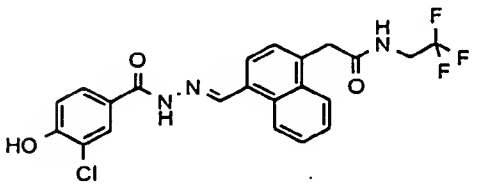


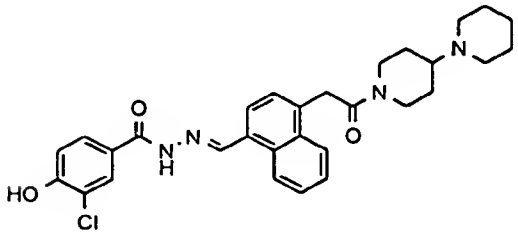


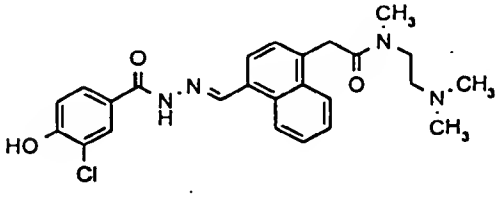


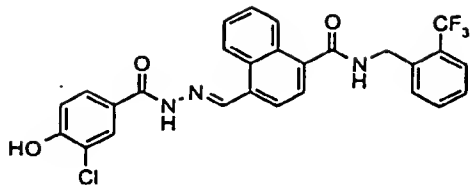


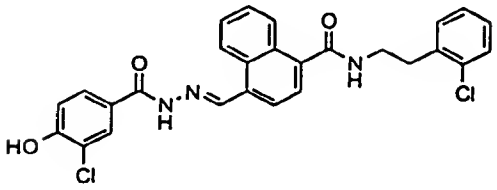


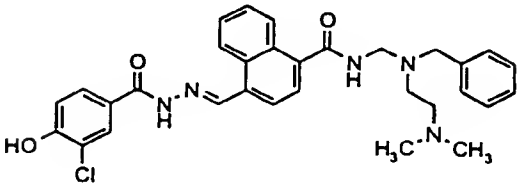


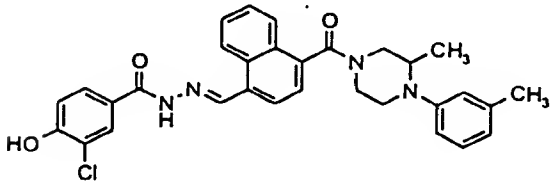


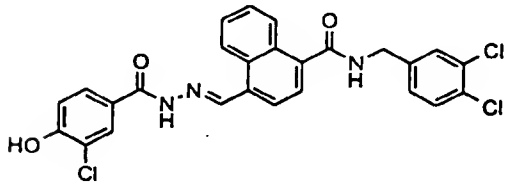


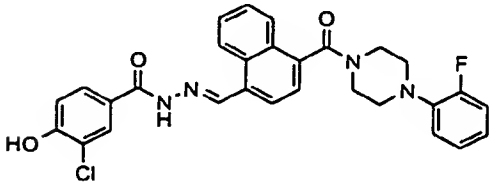


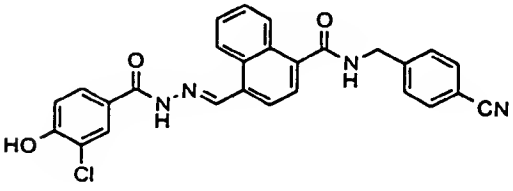


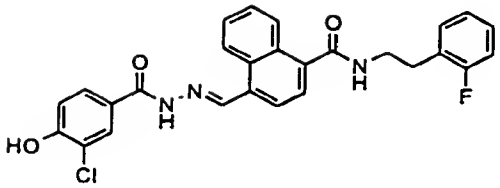


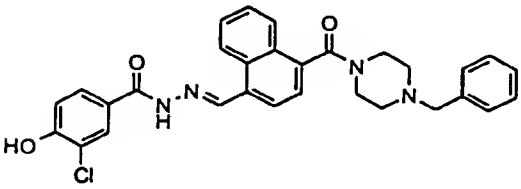


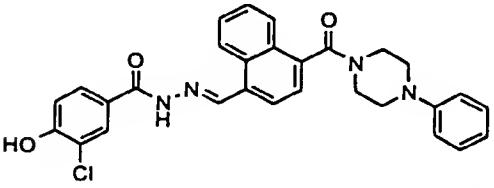


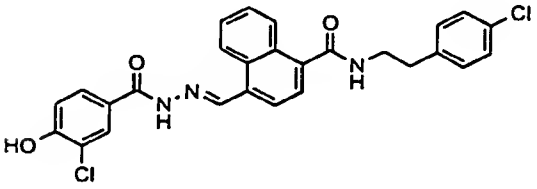


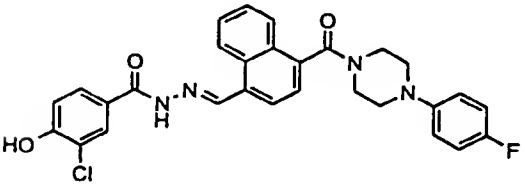


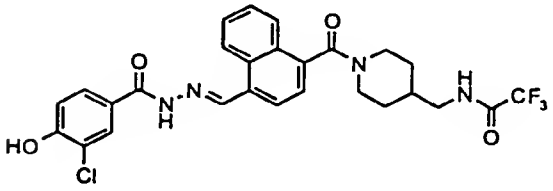


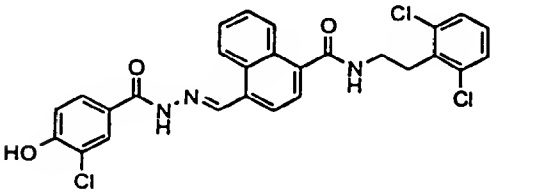


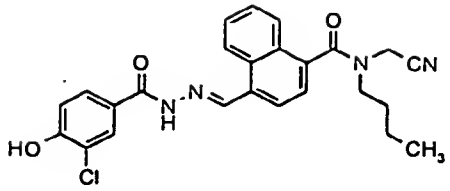


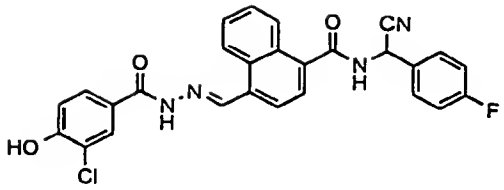


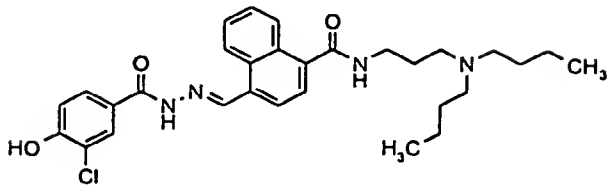


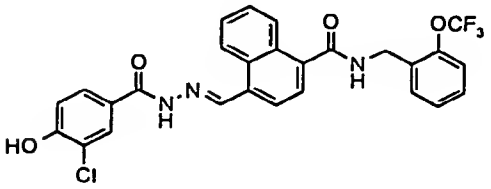


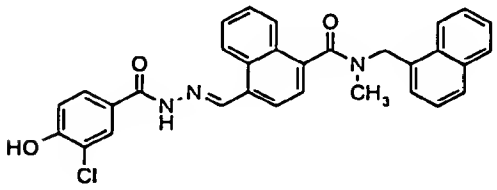


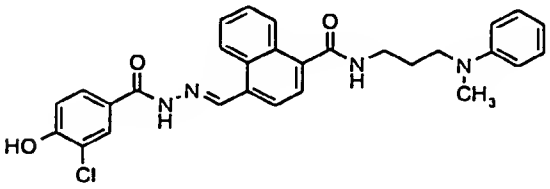


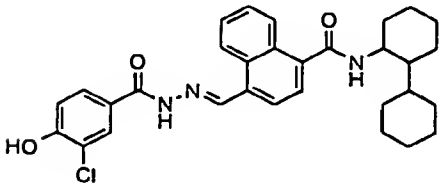


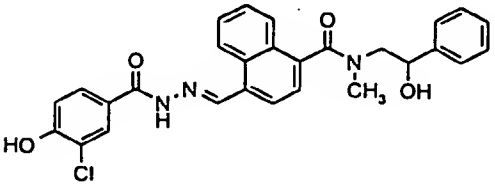


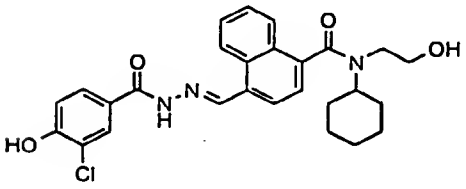


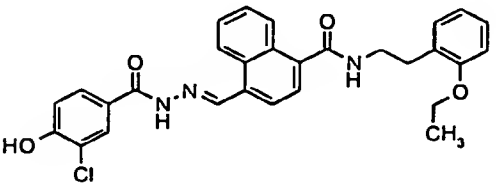


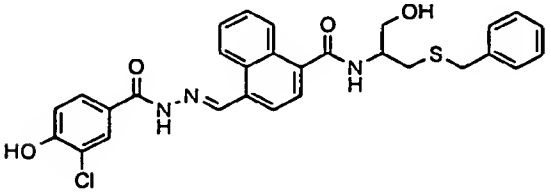


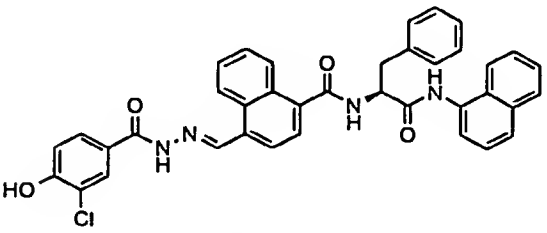


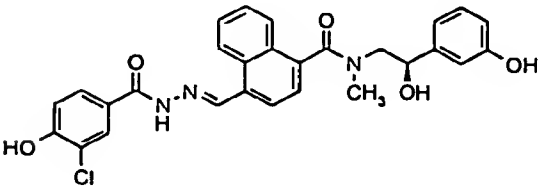


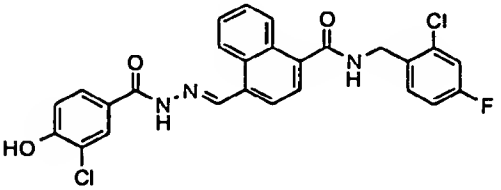


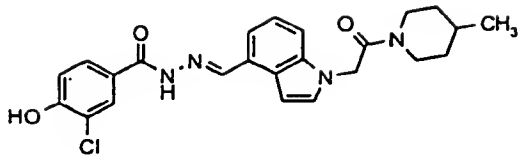


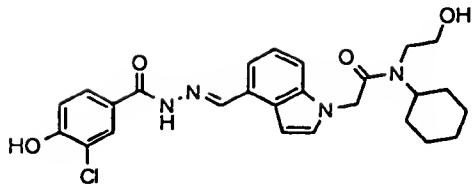


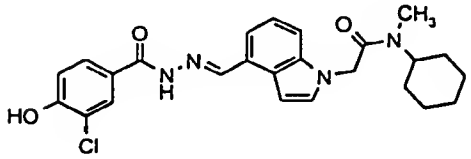


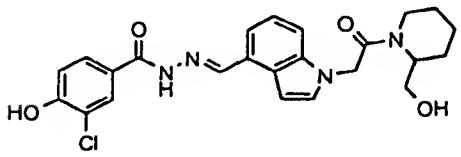


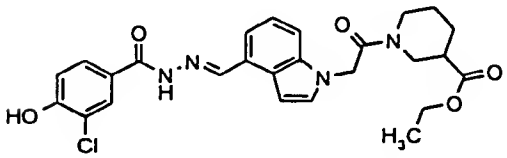


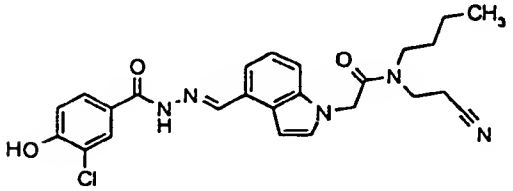


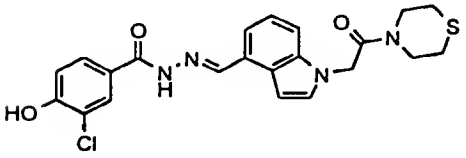


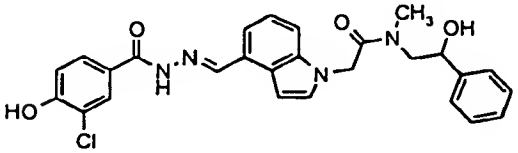


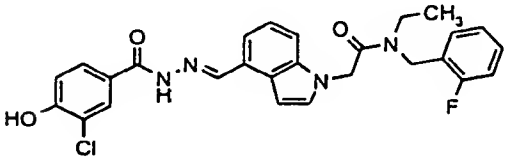


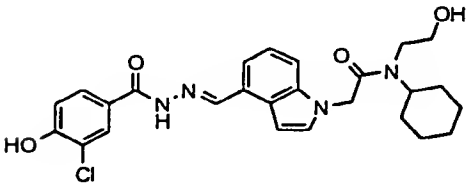


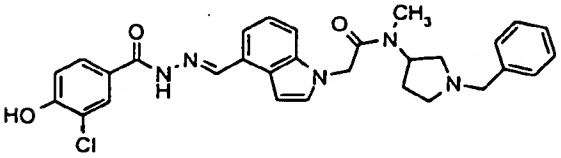


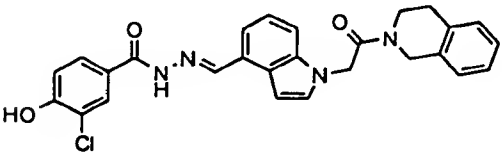


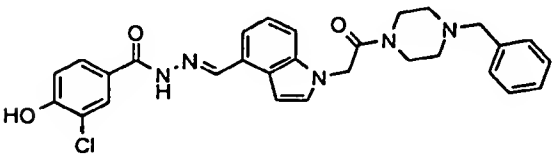


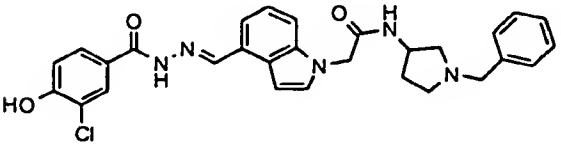


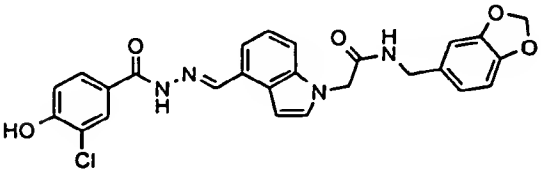


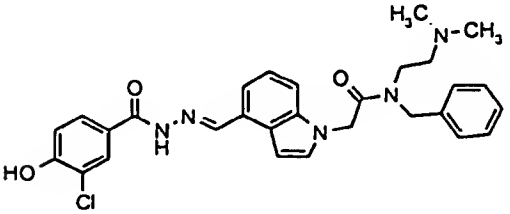


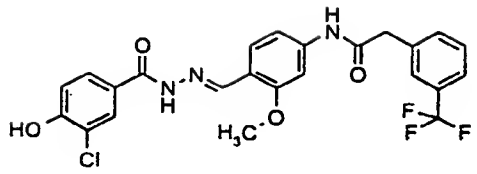


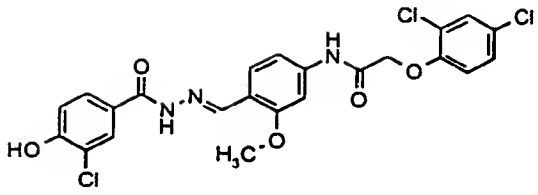


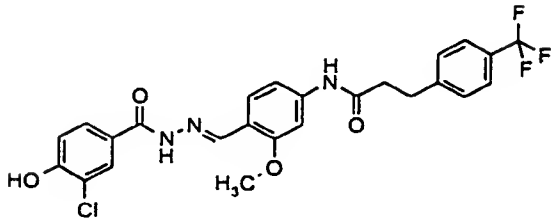


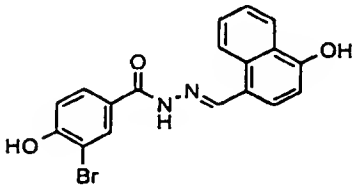


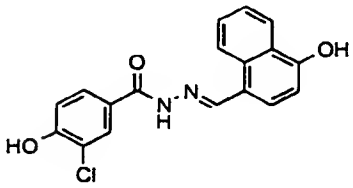


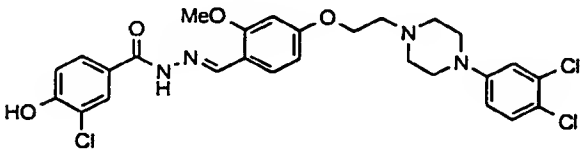


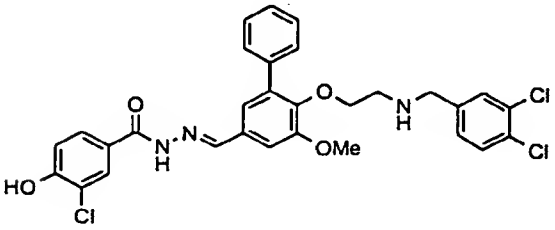


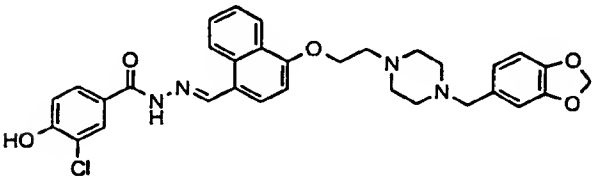


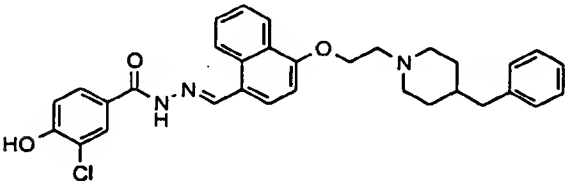


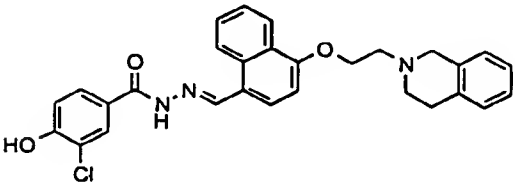


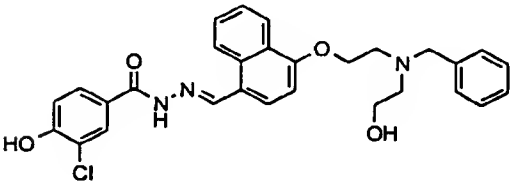


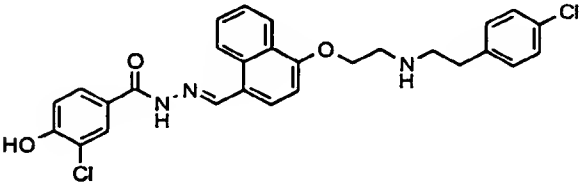


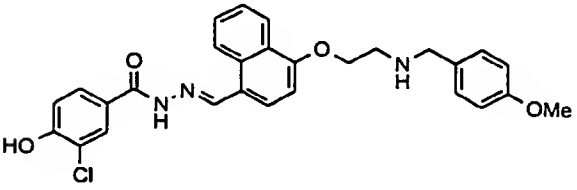


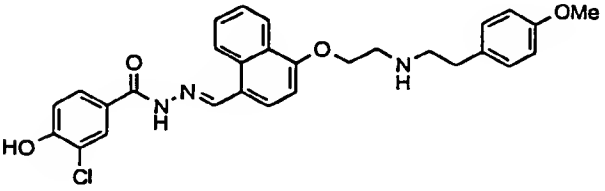


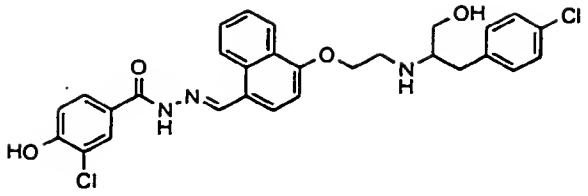


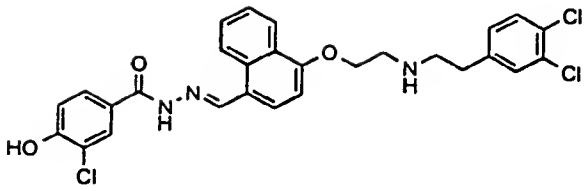


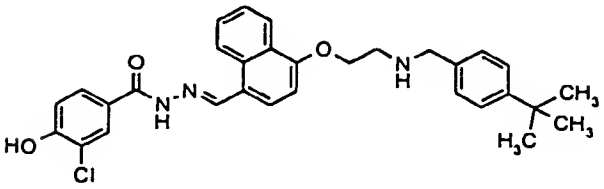


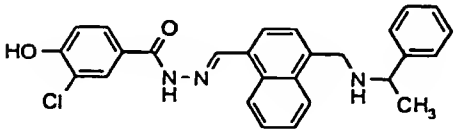


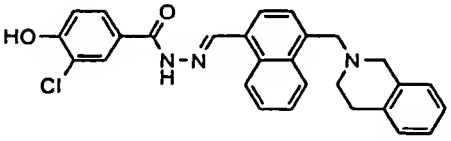


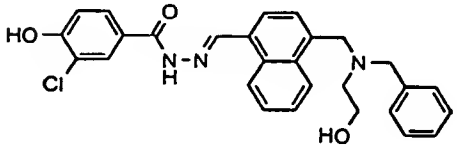


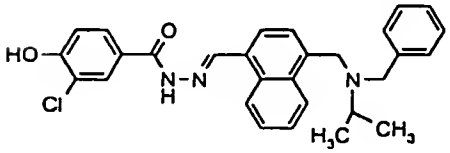


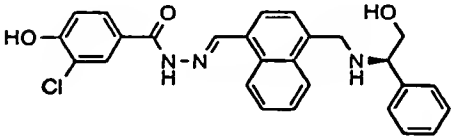


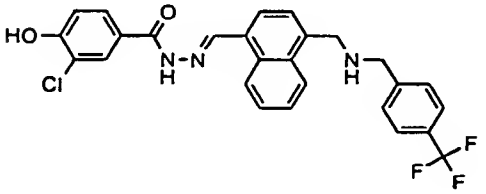


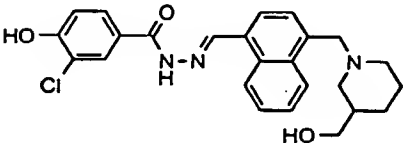


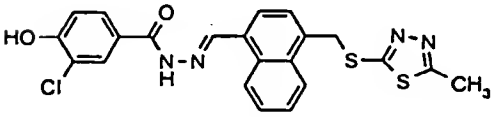


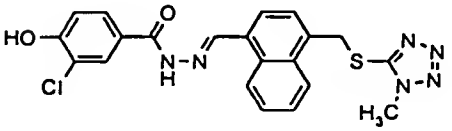


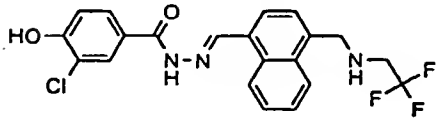


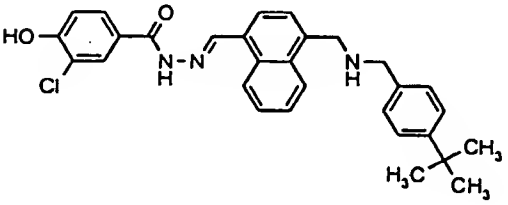


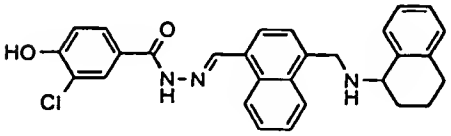


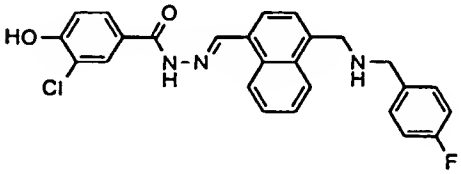


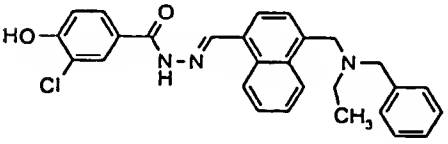


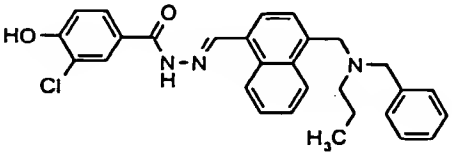


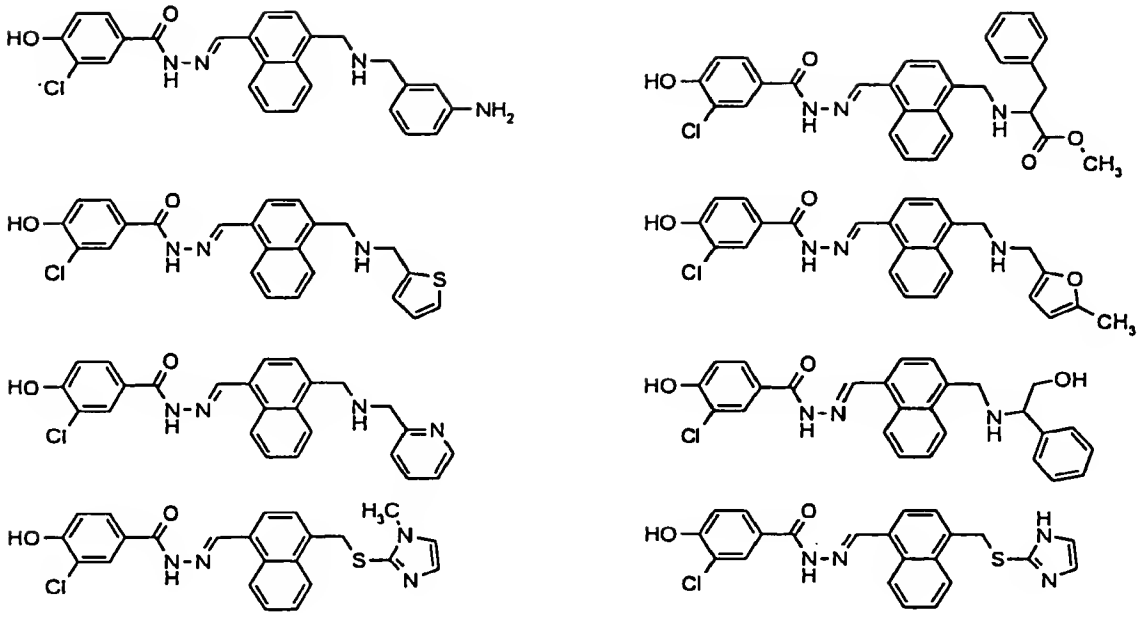








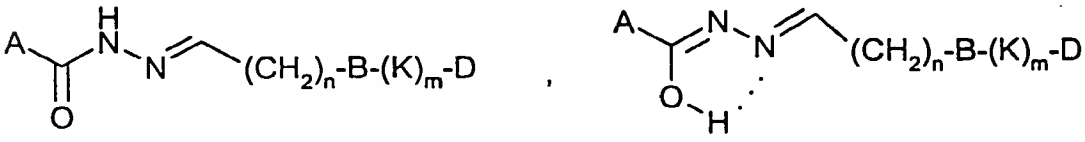




The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

Furthermore, one or more carbon-carbon or carbon-nitrogen double bonds may be present in the compounds which brings about geometric isomers. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included in the scope of the invention.

Furthermore, the compounds of the present invention may exist in different tautomeric forms, eg the following tautomeric forms:



It is intended that any tautomeric forms which the compounds are able to form are included in the scope of the present invention.

Pharmaceutical formulations and administration methods

The compounds according to the invention, which may also be referred to as an active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, pulmonal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal), the oral route being preferred. It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the condition to be treated, and the chosen active ingredient.

The compounds of the invention are effective over a wide dosage range. A typical dosage is in the range of from 0.05 to about 1000 mg, preferably of from about 0.1 to about 500 mg, such as of from about 0.5 mg to about 250 mg for administration one or more times per day such as 1 to 3 times per day. It should be understood that the exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated as well as other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are on the order of about 1/2 the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of formula I contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of formula I with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene salicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, pyruvic, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluensulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric or nitric acids. Physiologically acceptable salts of a

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more other pharmacologically active compounds, e.g. an antidiabetic or other pharmacologically active material, including compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism. Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S) which is incorporated herein by reference as well as orally active hypoglycaemic agents such as sulphonylureas, e.g. glibencla-

diluted in buffer and centrifuged at 40.000 * g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until required.

Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al, Hormone and Metab. Res. 4, 223-224 (1972). The specific activity was 460 μCi/μg on day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore). The buffer used in this assay was 25 mM HEPES pH 7.4 containing 0.1% human serum albumin (Sigma, grade V). Glucagon was dissolved in 0.05 M HCl, added equal amounts(w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.

175 μl of sample (glucagon or test compounds) was added to each well. Tracer (50.000 cpm) was diluted in buffer and 15 μl was added to each well. 0.5 μg freshly thawed plasma membrane protein diluted in buffer was then added in 15 μl to each well. Plates were incubated at 25°C for 2 hours. Non specific binding was determined with 10^{-6} M glucagon. Bound and unbound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed once with 150 μl buffer/ well. The plates were air dried for a couple of hours, whereafter filters were separated from the plates using a Millipore Puncher. The filters were counted in a γ counter.

Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc). The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM $MgSO_4$, 1.7 mM ATP, 20 μM GTP, 2 mM IBMX, 0.02% tween-20 and 0.1% HSA. pH was 7.4 Glucagon and proposed antagonist were added in 35 μl diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM $MgSO_4$, 0.0222 % tween-20 and 0.111 % HSA, pH 7.4. 20 μl of 50 mM tris/HCl, 1 mM EGTA, 1.5 mM $MgSO_4$, 11.8 mM ATP, 0.14 mM GTP, 14 mM iso-buthyl-methyl-xanthine (IBMX) and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

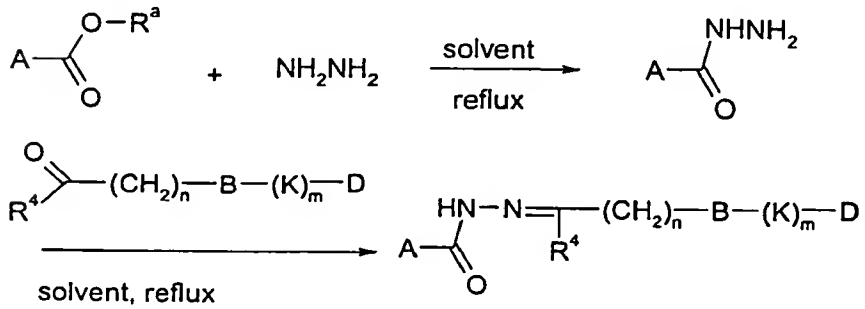
Functional Assay (II)

The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM $MgCl_2$, 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM NaH_2PO_4, 3mM glucose and 0.2% BSA. The pH was 7.4. Loose whole cells (0.5 ml, 10^6/ml) were pretreated with various concentrations of compounds for 10 min at 37°C, then challenged with glucagon for 20 min. Some aliquots (500 µL) of cells were treated with test compounds (55 uL) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500 µl 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

General procedures for the preparation of alkylidene hydrazides:

The compounds of general formula I may be prepared according to one embodiment of the invention, the alkylidene hydrazides of general formula II, as indicated in Scheme I, that is, by converting an ester of a carboxylic acid, for example, an aromatic acid to a hydrazide derivative and further reacting that product compound with a substituted aldehyde or ketone to yield a substituted alkylidene hydrazide.

SCHEME I



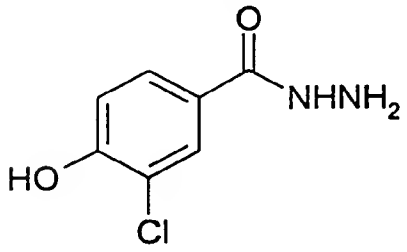
wherein A, B, K, D, m, n and R^4 are as defined for formula I and R^a is lower alkyl.

General procedure for the synthesis of precursor hydrazides A-(C=O)-$NHNH_2$:

The reaction is known (Org. Syn., Coll. Vol. II, A.H.Blatt, ed., John Wiley & Sons, New York, 1943, p. 85; Org. Syn., Coll. Vol. IV, N. Rabjohn, ed., John Wiley & Sons, New York, 1963, p. 819) and is generally performed by stirring the corresponding ester (either methyl, ethyl or other lower alkyl ester) with 2-10 molar excess of hydrazine in the presence of a solvent such as ethyl alcohol, methyl alcohol, isopropyl or tert-butyl alcohol or tetrahydrofuran, dioxane, DMSO, ethylene glycol, ethylene glycol dimethyl ester, benzene, toluene or a mixture of the above solvents or, in the absence of a solvent where excess of hydrazine acts as a solvent. The reactions are performed between 0°C to 130°C, preferably between 20°C to 100°C, most preferably at or about the reflux temperature of the solvent. The reactions are preferably conducted under an inert atmosphere such as N_2 or Ar. When the reaction is complete as judged by disappearance of the starting ester by TLC or HPLC, the solvent may be removed by concentration at atmospheric or reduced pressure.

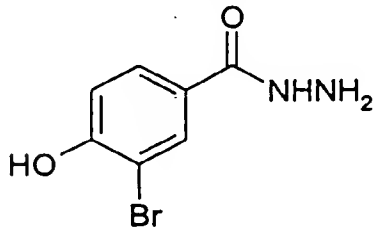
Preparation of 3-chloro-4-hydroxybenzoic acid hydrazide:

To a sample of methyl 3-chloro-4-hydroxybenzoate (2 g) dissolved in ethanol (50 mL) was added hydrazine (1.8 mL). The reaction was refluxed overnight under nitrogen. Upon cooling the reaction vessel, the desired product crystallized out of solution. The white solid was isolated by filtration. Recrystallization from hot ethanol gave the 3-chloro-4-hydroxybenzoic acid hydrazide in 60% yield.



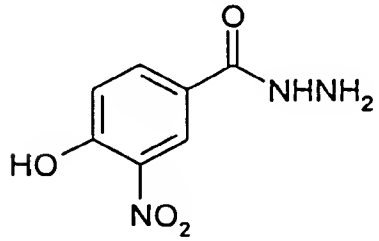
^{1}H NMR (DMSO-d$_6$): δ 4.49 (broad s, 2H), 7.05 (dd, 1H), 7.71 (dd, 1H), 7.89 (d, 1H), 9.669 (s, 1H), 10.72 (broad s, 1H).

By use of the above methodology, other hydrazides useful as intermediates in preparing the compounds of the invention are prepared, for example:



3-Bromo-4-hydroxybenzoic acid hydrazide

^{1}H NMR (DMSO-d$_6$): δ 9.95 (s, 1H), 9.65 (d, 1H), 9.61 (broad s, 1H), 6.95 (d, 1H), 4.40 (broad s, 2H); MS m/z 233.1.



$CuSO_4$ (100-200 mg) was added and the mixture was heated to 90 °C until evolution of gas stopped. After cooling, the mixture was extracted with ethyl ether (3x). The combined organic fractions were extracted with 3N NaOH (3x). The combined aqueous layer was acidified with conc. HCl and the product was extracted with ethyl ether (3x). The organic fractions were washed with water, brine, and dried over $MgSO_4$. The crude product was introduced into a silica gel column and eluted with ethyl acetate/hexane (1/1) to afford 2-chloro-4-hydroxybenzoic acid.

^{1}H NMR (DMSO-D6): δ 6.97 (dd, 1H), 7.05 (d, 1H), 7.95 (d, 1H), 10.90 (brd s, 1H).

Step B:

To a solution 2-chloro-4-hydroxybenzoic acid in anhydrous methanol was added thionyl chloride (1.5 eq). After stirring the solution at room temperature for 16 hours, the solvent was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and dried over $MgSO_4$ and concentrated in vacuo to give methyl 2-chloro-4-hydroxybenzoate.

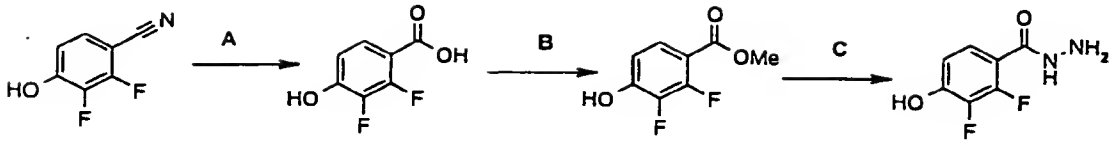
Step C:

To a solution of methyl 2-chloro-4-hydroxybenzoate (13.6 g, 73.1 mmol) in acetic acid (300 mL) was added N-chlorosuccinimide (9.8 g, 73.7 mmol). The solution was refluxed for 24 h and the solvent was evaporated under vacuo. The residue was taken up in chloroform, washed with water, brine, dried over magnesium sulfate, filtered and concentrated. Methyl 2,3-dichloro-4-hydroxybenzoate precipitated out of ethyl acetate. Chromatography of the residue using ethyl acetate/hexane (1/9 to 3/7) afforded methyl 2,5-dichloro-4-hydroxybenzoate (1.4 g, 60%) as well as an additional batch of methyl 2,3-dichloro-4-hydroxybenzoate isomer (total of 8.4 g, 10%).

Methyl 2,3-dichloro-4-hydroxybenzoate:

^{1}H NMR (DMSO-D6) δ 3.81 (s, 3H), 7.02 (d, 1H), 7.70 (d 1H), 11.52 (s, 1H); MS (APCI): 221, 223.

Methyl 2,5-dichloro-4-hydroxybenzoate:



Step A:

A mixture of 2,3-difluoro-4-cyanophenol (1 g, 6.45 mmol) in water (8 mL), H_2SO_4 (8 mL), and acetic acid (8 mL) was refluxed for 48 hours. The solvents were removed by rotary evaporation to give a slurry which was poured onto ice. The product precipitated out of solution and filtered. The solid was washed with water and dried to give 2,3-difluoro-4-hydroxybenzoic acid (800 mg, 71%).

^{1}H NMR (DMSO-D_6): δ 6.87 (t, 1H), 7.60 (t, 1H), 11.28 (s, 1H), 12.53 (brd s, 1H).

Step B:

To the 2,3-difluoro-4-hydroxybenzoic acid (800 mg, 5.1 mmol) dissolved in anhydrous methanol (50 mL) was added thionyl chloride (0.55 mL, 7.3 mmol). After stirring the solution at room temperature for 16 hours, the solvent was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and dried over $MgSO_4$ to give methyl 2,3-difluoro-4-hydroxybenzoate (540 mg, 62%).

^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H), 6.34 (brd s, 1H), 6.82 (dt, 1H), 7.68 (dt, 1H).

Step C:

The 2,3-difluoro-4-hydroxybenzoic acid hydrazide was prepared from the methyl 2,3-difluoro-4-hydroxybenzoate above according to the general procedure for the synthesis of precursor hydrazides A-(C=O)-$NHNH_2$. The product was purified via silica gel column chromatography using CH_2Cl_2/MeOH (95/5 to 80/20) to afford the title compound.

^{1}H NMR (DMSO-D_6): δ 4.48 (s, 2H), 6.80 (m, 1H), 7.22 (m, 1H), 9.36 (s, 1H), 10.89 (s, 1H); MS (APCI): 189.

mixture of 50 mL of ethyl acetate and a ferric chloride solution (4 g of hydrated ferric chloride in 7 mL of conc. hydrochloric acid). The ethyl acetate layers were combined, washed with brine containing sodium metabisulfite, dried over sodium sulfate, filtered, and the solvent removed in vacuo. The resulting solids were purified by flash chromatography on silica gel (20% ethyl acetate/ hexane) to afford methyl-3-cyano-4-hydroxybenzoate, 0.93g (73%).

^{1}H NMR (DMSO- D_6): δ 3.79 (s, 3H), 7.07 (d, J = 8.7, 1H), 8.02 (dd, J = 8.7, 1.9, 1H), 8.10 (d, J = 1.9, 1H).

Step C:

Methyl-3-cyano-4-hydroxybenzoate (2.71g, 15.3 mmol) was dissolved in 50 mL of THF. The solution was chilled in an ice bath, and 2.0M potassium hydroxide (17 mL, 34 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight. TLC indicated complete reaction. The THF was removed by rotary evaporation. The aqueous residue was acidified with aqueous trifluoroacetic acid and purified by reverse-phase HPLC (C-18, 0.1% TFA in water and acetonitrile). 3-Cyano-4-hydroxybenzoic acid was obtained as a white powder (2.1g, 84%) after lyophilization.

^{1}H NMR (DMSO- D_6): δ 7.09 (d, J = 9.0, 1H), 8.00 (dd, J = 9.0, 2.3, 1H), 8.07 (d, J = 2.3, 1H) 12.50 (br s, 2H); MS (APCI, neg): 162. IR: 2252 cm^{-1}, CN.

Step D:

3-Cyano-4-hydroxybenzoic acid (1.88g, 11.5 mmol) was dissolved in 20 mL of methylene chloride/DMF (1/1) and chilled in an ice-bath. Diisopropylethylamine (12 mL, 69 mmol), t-butyl carbazate (1.76g, 13.3 mmol), and PyBroP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 6g, 12.9 mmol) were added, and the mixture was stirred to form a clear solution. The solution stood in the refrigerator overnight. TLC indicated that the reaction was not complete, so additional diisopropylethylamine (22 mL, 127 mmol), t-butyl carbazate (0.85g, 6.4 mmol) and PyBroP (3.0g, 6.4 mmol) were added. After 8 more hours at 0 °C, the reaction was worked up as follows. The solution was reduced by rotary evaporation. The remaining DMF solution was diluted with 100 mL of ethyl acetate, and washed with several portions of 0.1 M HCl (until the wash remained acidic to litmus paper). The ethyl acetate layer was further washed with 3 portions of brine, dried over magnesium sulfate, filtered, and

To the silver oxide above was added 1N NaOH (150 mL) and 4-hydroxynaphthaldehyde (1 g, 6 mmol)). The mixture was heated to 70 °C for 10 minutes after which additional amounts of 4-hydroxynaphthaldehyde (5.5 g, 32 mmol) was added in portions. The mixture was kept at 80 °C for 16 hours. TLC analysis indicated incomplete conversion. An additional portion of silver oxide was prepared as above and added to the reaction mixture. After heating the mixture for an additional 6 hours, the mixture was cooled and acidified with 1N HCl. The aqueous layer was extracted with ethyl acetate (3x) and upon concentration 4-hydroxynaphthoic acid precipitated (3.7 g, 60%) out of solution.

^{1}H NMR (DMSO-D6): δ 6.69 (d, 1H), 7.28 (t, 1H), 7.39 (t, 1H), 7.93 (d, 1H), 8.03 (d, 1H), 8.82 (d, 1H), 10.82 (s, 1H), 12.29 (s, 1H).

Step B:

To a solution 4-hydroxynaphthoic acid in anhydrous methanol at 0 °C was added thionyl chloride (1.5 eq). After stirring the solution at room temperature for 16 hours, the solvent was evaporated. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and dried over $MgSO_4$ to give methyl 4-hydroxynaphthoate.

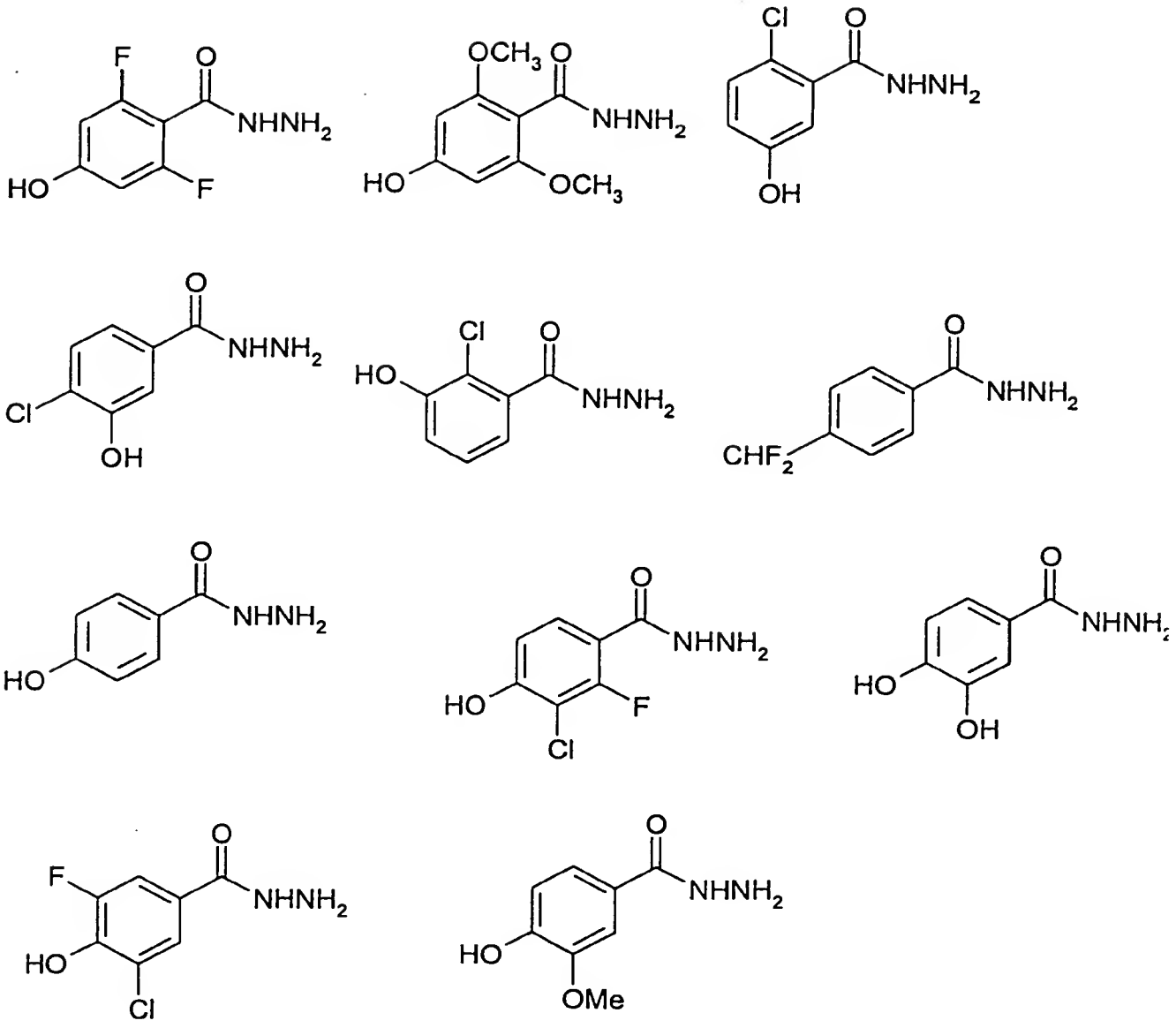
^{1}H NMR (DMSO-D6): δ 3.87 (s, 3H), 6.92 (d, 1H), 7.53 (t, 1H), 7.65 (t, 1H), 8.13 (d, 1H), 8.26 (d, 1H), 8.93 (d, 1H), 11.16 (s, 1H).

Step C:

The title compound was prepared from methyl 4-hydroxynaphthoate according to the procedure for the synthesis of precursor hydrazides A-(C=O)-$NHNH_2$.

^{1}H NMR (DMSO-D6): δ 6.60 (d, 1H), 7.28 (m, 3H), 7.95 (d, 1H), 8.07 (d, 1H), 9.25 (brd s, 1H).

Moreover, by use of the above methodology, the following hydrazides useful as intermediates in preparing the compounds of the invention may be prepared:



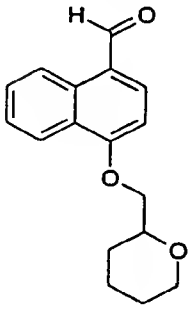
General procedure for the synthesis of ether-substituted aryl-aldehydes:

The ether-linked aldehydes may be prepared by 0-alkylation of the corresponding phenolic compounds using various electrophilic alkylating agents that introduce the -$(K)_m$-D moiety as defined above in a reaction generally known as Williamson ether synthesis (H. Feuer, J. Hooz in The Chemistry of the Ether Linkage, S. Patai Ed., Wiley, New York 1967, p. 446-460).

ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture. Specific examples illustrating the preparation of ether-substituted aryl-aldehydes are provided below.

Preparation of 4-(2-tetrahydropyranylmethoxy)-1-naphthaldehyde:

A mixture of 4-hydroxynaphthaldehyde (1 g, 5.8 mmol), 2-bromomethyl tetrahydropyran (1 g, 5.8 mmol) and powdered K_2CO_3 (1.2 g, 8.7 mmol) in dimethyl formamide was stirred at 60°C overnight. The mixture was taken up in water and ethyl acetate. The organic layer was separated and washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by silica gel column chromatography using ethyl acetate/hexane.

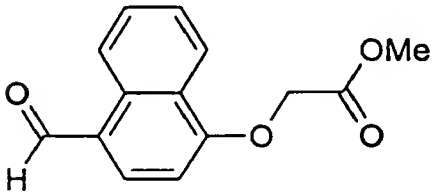


^{1}H NMR (DMSO-d_6): δ 1.48 (m, 4H), 1.74 (d, 1H), 1.84 (m, 1H), 3.44 (m, 1H), 3.78 (m, 1H), 3.92 (d, 1H), 4.23 (m, 2H), 7.17 (d, 1H), 7.64 (t, 1H), 7.74 (t, 1H), 8.11 (d, 1H), 8.27 (d, 1H), 9.22 (d, 1H), 10.17 (s,1H).

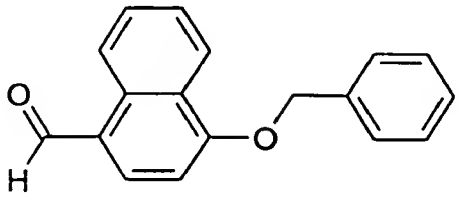
Preparation of 4-[(3,5-bis-trifluoromethyl)benzyloxy]-1-naphthaldehyde:

A mixture of 4-hydroxynaphthaldehyde (1 g, 5.8 mmol), 3,5-bis-trifluoromethylbenzylbromide (1.8 g, 5.8 mmol), and powdered K_2CO_3 (1.2 g, 8.7 mmol) was stirred in acetone (40 mL) overnight. The mixture was poured onto 200 mL of ice-chips and stirred until the ice melted. The yellow precipitate, 4-((3,5-bis-trifluoromethyl)benzyloxy)-1-naphthaldehyde, was collected and dried.

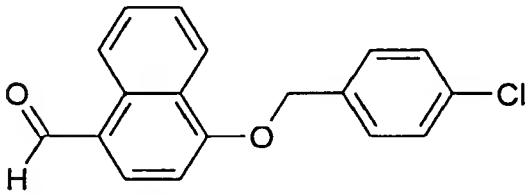
By application of the above methodology the following substituted aldehyde intermediates were synthesized:



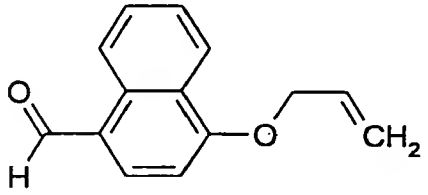
4-carbomethoxymethoxy-1-naphthaldehyde
m.p.: 115-116°C



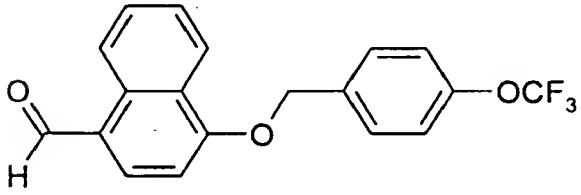
4-benzyloxy-1-naphthaldehyde



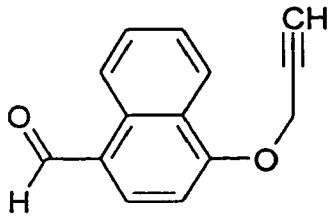
4-(4-chlorobenzyloxy)-1-naphthaldehyde



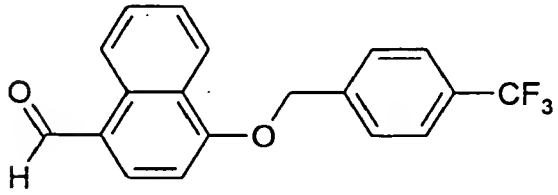
4-allyloxy-1-naphthaldehyde



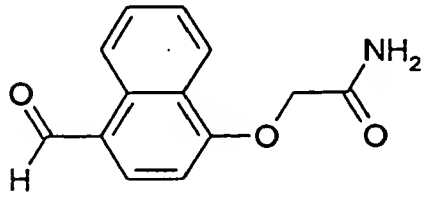
4-(4-trifluoromethoxybenzyloxy)-1-naphthaldehyde



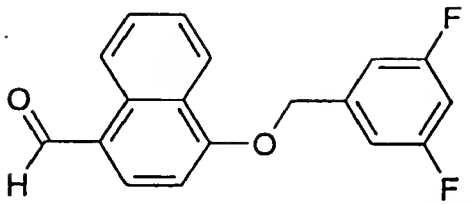
4-propargyloxy-1-naphthaldehyde



4-(4-trifluoromethylbenzyloxy)-1-naphthaldehyde

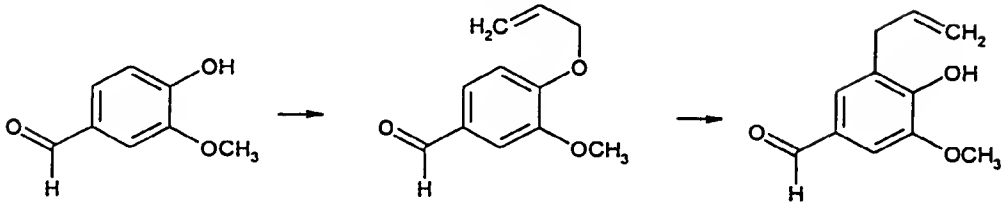


2-[(4-carboxaldehydo)-1-naphthyloxy]acetamide
m.p. 174-175°C



4-(3,5-difluorobenzyloxy)-1-naphthaldehyde
m.p. 100-101°C

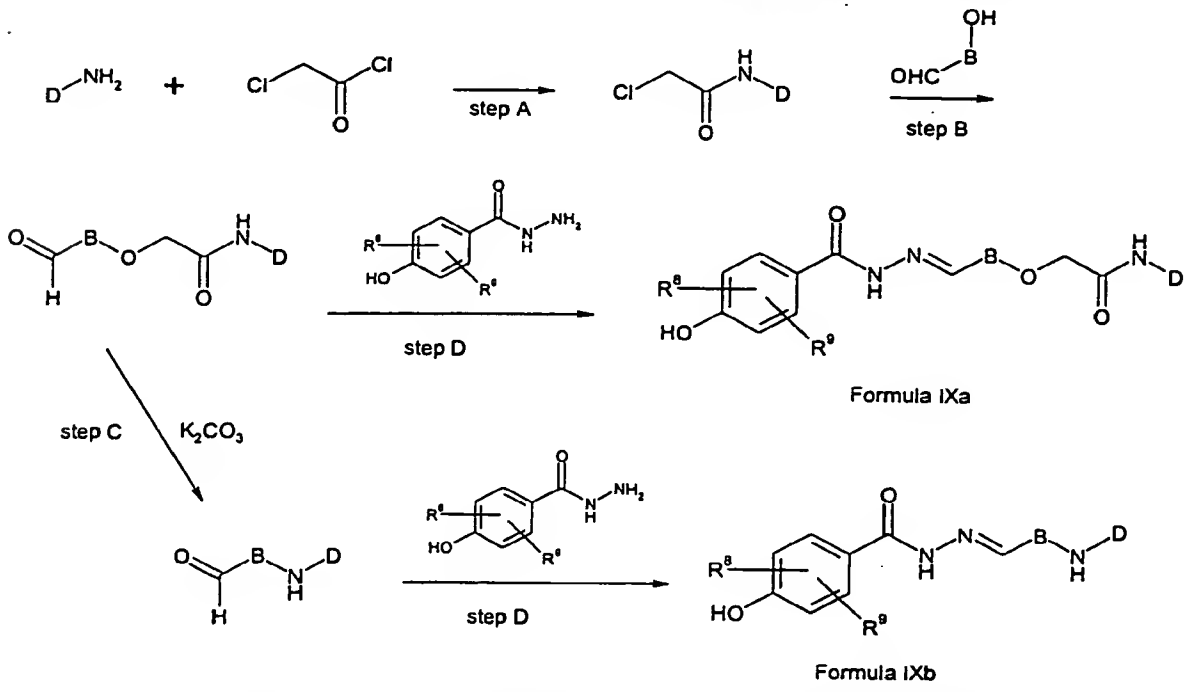
Preparation of 3-Allyl-4-hydroxy-5-methoxy-benzaldehyde:



To a solution of vanillin (1.0 g, 6.57 mmol) in acetone (30 mL) was added potassium carbonate (4.50 g, 32.8 mmol) and allyl bromide (0.62 mL, 7.3 mmol). The mixture was heated under reflux for 6 h. TLC showed appearance of a new spot. Potassium salts were removed by filtration and the filtrate was concentrated to a syrup. A small sample was purified using prep TLC using hexane/ethyl acetate 7:3 as developing solvent. ^{1}H NMR ($CDCl_3$) δ = 3.94 (s, 3H), 4.67 - 4.83 (m, 2H), 5.30 - 5.55 (m, 2H), 6.01 - 6.21 (m, 1H), 6.98 (d, J = 9 Hz, 1H), 7.40 - 7.56 (m, 2H), 9.85 (s, 1H); MS (APCI): 193.6

The crude syrup was heated neat in an oil bath at 200 °C for 6 h. The crude material was dissolved in chloroform and filtered through a pack of silica gel. The crude product (yield 72%) was used as is in the next step for O-alkylation. A small portion was purified using prep-TLC to give a pure sample of 3-allyl-4-hydroxy-5-méthoxy-benzaldehyde. ^{1}H NMR ($CDCl_3$) δ = 3.46 (d, J = 6 Hz, 2 H), 3.96 (s, 3H), 5.02 - 5.22 (m, 2H), 5.94 - 6.11 (m, 1H), 6.30 (s, 1H), 7.45 (s, 2H), 9.80 (s, 1 H); MS (APCI): 193.3.

General procedure for the synthesis of compounds of formulae IXa and IXb:



In the above formulae B, D, R^8 and R^9 have the same meanings as defined for formula I.

Step A:

To a solution of aniline (or an aniline derivative) (1 eq.) in THF was added dropwise chloroacetyl chloride (1.2 eq.). After stirring at room temperature overnight, 100 mL water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed twice with dilute hydrochloric acid, twice with water, dried over $MgSO_4$ and then concentrated to give pure product.

Step B:

To a solution of chloroacetanilide (or a derivative thereof) (1.2 eq.) and 2-methoxy-4-hydroxy benzaldehyde (or another aromatic aldehyde substituted with a hydroxy group) (1 eq.) in DMSO was added potassium carbonate (1.5 eq.). After stirring overnight at room temperature, 100 ml water was added. The mixture was extracted with ethyl acetate, the organic extracts were washed twice with a satd. sodium bicarbonate solution, twice with water, and dried over $MgSO_4$. After concentration in vacuo, the product was obtained.

Step C:

The mixture of aldehyde (1 eq.) and potassium carbonate (1.5 eq.) in acetonitrile was refluxed. The reaction was monitored by TLC (hexane : ethyl acetate = 2:1). When TLC showed almost complete conversion (about 48 h), 100 ml water was added. The mixture was extracted with ethyl acetate, the organic extracts were dried over $MgSO_4$, and concentrated to give the desired product which can be further purified by column chromatography, or used directly for the next step.

The following two aldehydes were prepared as examples of compounds that can be prepared using this methodology:

4-(4-Chlorophenylamino)-2-methoxybenzaldehyde:

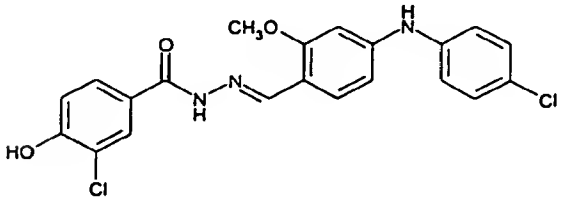
Prepared from N-(4-chlorophenyl)-2-(4-formyl-3-methoxyphenoxy)acetamide using the procedure described in step C above.

vents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate to give a compound of formula IXb.

The following compounds of formulae IXa or IXb according to the invention were prepared as examples of compounds that can be prepared using this methodology:

EXAMPLE 1:

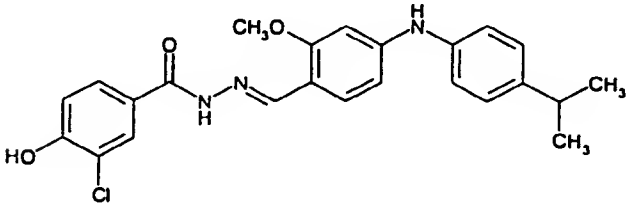
3-Chloro-4-hydroxybenzoic acid [4-(4-chlorophenylamino)-2-methoxybenzylidene]hydra-zide



^{1}H NMR (DMSO-D6): δ 3.81 (s, 3H), 6.72-6.67 (m, 2H), 7.04 (d, J = 8.5Hz, 1H), 7.17 (d, J = 8.7Hz, 2H) 7.31 (d, J = 8.7Hz, 2H), 7.77- 7.70 (m, 2H), 7.96 (d, J = 1.6Hz, 1H), 8.65 (s, 1H), 8.70 (s, 1H), 10.87 (s, 1H), 11.51 (s, 1H); MS (APCI): 430.

EXAMPLE 2:

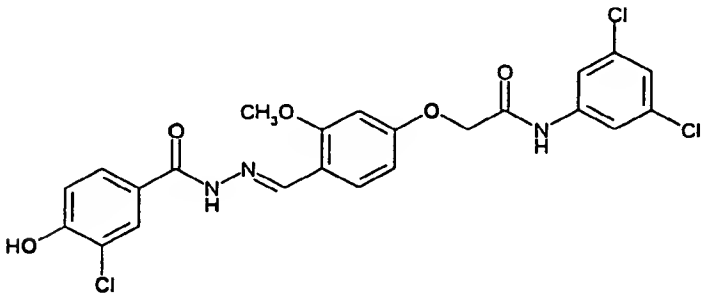
3-Chloro-4-hydroxybenzoic acid [4-(4-isopropylphenylamino)-2-methoxybenzylidene]hydrazide



^{1}H NMR (DMSO-D$_6$): δ 1.18 (2s, 6H), 2.86 (m, 1H), 3.79 (s, 3H), 6.65 (m, 2H), 7.03 (d, 1H), 7.11 (d, 2H), 7.19 (d, 2H), 7.70 (d, 1H), 7.75 (dd, 1H), 7.97 (s, 1H), 8.49 (s, 1H), 8.64 (s, 1H), 10.88 (s, 1H), 11.48 (s, 1H); MS (FAB): 438.16.

EXAMPLE 5:

2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenoxy}-N-(3,5-dichlorophenyl)acetamide



^{1}H NMR (DMSO-D6): δ 4.06 (s, 3H), 4.94 (s, 2H), 6.8 (d, 1H), 6.88 (s, 1H), 7.20 (d, 1H), 7.45 (s, 1H), 7.90 (m, 3H), 8.10 (s, 1H), 8.82 (s, 1H), 10.62 (s, 1H), 11.07 (brd s, 1H), 11.75 (s, 1H); MS (APCI): 524.8.

General procedure for the synthesis of alkylidene hydrazides of formula II according to the invention:

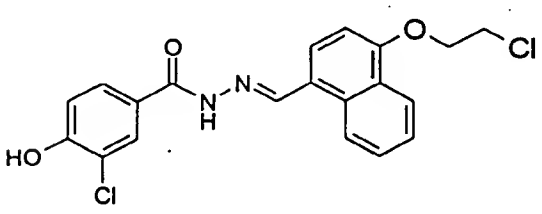
The acylhydrazides are treated with the corresponding carbonyl compounds, such as aldehydes or ketones, in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/-methanol or dichloromethane/methanol or chloroform/ethyl acetate. The product is isolated by concentration in vacuo of the appropriate fractions. Specific examples illustrating the preparation of compounds according to the invention are provided below.

vacuo to give the crude product. The product was purified by silica gel column chromatography using CH_2Cl_2/MeOH as the mobile phase.

^{1}H NMR (DMSO-d_6): δ 3.77 (s, 6H), 4.91 (s, 2H), 6.95 (s, 2H), 6.99 (d, 1H), 7.30 (d, 2H), 7.52 (d, 2H), 7.68 (m, 1H), 7.89 (s, 1H), 8.29 (s, 1H), 10.90 (broad s, 1H), 11.69 (s, 1H); MS (ESI): m/z 525.37 $(M+H)^+$.

EXAMPLE 8:

3-chloro-4-hydroxybenzoic acid [4-(2-chloroethoxy)-1-naphthylmethylene]hydrazide



A solution of 1-(4-chloroethoxy)naphthaldehyde (2.35 g, 10 mmoles), 3-chloro-4-hydroxy benzoic acid hydrazide (1.87g, 10 mmoles), glacial acetic acid (0.2 mL) and dimethylsulfoxide (DMSO)(15 mL) was stirred at room temperature overnight. Ethyl acetate (100 mL) was added. The solution was extracted with water and brine which induced precipitation. The product (3.1 g, 77% yield) was obtained by suction filtration. The product was purified by recrystallization from ethyl acetate.

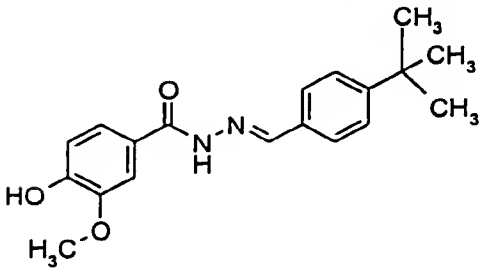
MS (CI): 235. ^{1}H NMR (DMSO-d_6): δ 11.5 (s, 1H), 10.7 (s, 1H), 8.7 (bs, 2H), 8.1 (m, 1H), 7.8 (s, 1H), 7.6-7.3 (m, 2H), 7.0 (m, 2H), 4.3 (t, 2H), 3.7 (t, 2H).

By application of the above methodology the following compounds of the invention are synthesized employing the following general procedure:

To a solution of 1 mmol of an arylcarboxylic acid hydrazide in 2 ml of anhydrous DMSO was added 1 mmol of the carbonyl compound (an aldehyde or ketone), followed by a catalytic amount of glacial acetic acid. The reaction was stirred overnight under nitrogen and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water, brine, and dried over $MgSO_4$. Upon partial concentration of the solvent in vacuo, the alkylene

EXAMPLE 11:

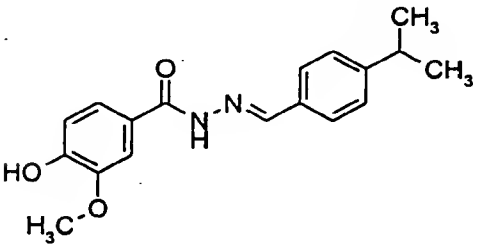
4-Hydroxy-3-methoxybenzoic acid (4-tert-butylbenzylidene)hydrazide



^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9 H), 3.91 (s, 3 H), 6.16 (s, 1 H), 6.88 (d, 1 H), 7.23 - 7.78 (m, 6 H), 8.28 (s, 1 H), 9.58 (s, 1 H). MS (APCI): 327.

EXAMPLE 12:

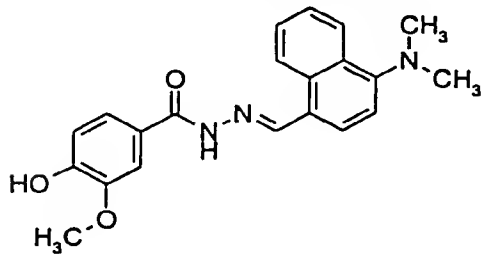
4-Hydroxy-3-methoxybenzoic acid (4-isopropylbenzylidene)hydrazide



^{1}H NMR ($CDCl_3$) δ 1.29 (d, 6 H), 2.94 (q, 1 H), 3.98 (s, 3 H), 6.13 (s, 1 H), 6.97 (d, 1 H), 7.20 - 7.80 (m, 6 H), 8.29 (s, 1 H), 9.38 (s, 1 H). MS (APCI): 313

EXAMPLE 15:

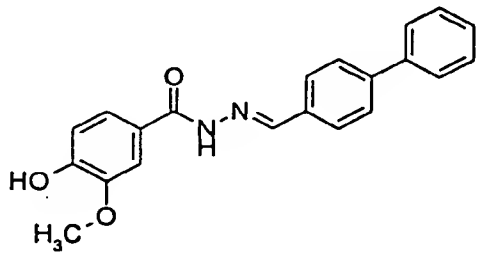
4-Hydroxy-3-methoxybenzoic acid (4-dimethylamino-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 3.05 (s, 6 H), 4.03 (s, 3 H), 7.06 (d, J = 8.1 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.63 - 7.80 (m, 4 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.38 (d, J = 7.9 Hz, 1 H), 9.10 (d, J = 8.4 Hz, 1 H), 9.15 (s, 1 H), 9.90 (s, 1 H), 11.73 (s, 1 H). MS (APCI): 364.

EXAMPLE 16:

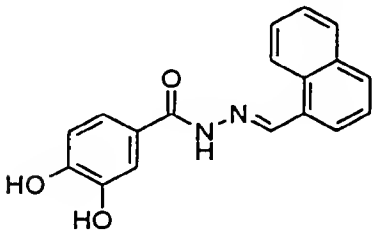
4-Hydroxy-3-methoxybenzoic acid (4-phenylbenzylidene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 4.02 (s, 3 H), 7.04 (d, J = 8.2 Hz, 1 H), 7.63 - 7.68 (m, 5 H), 7.88 - 7.96 (m, 6 H), 8.64 (s, 1 H), 9.91 (s, 1 H), 11.83 (s, 1 H). MS (APCI): 347.

EXAMPLE 19:

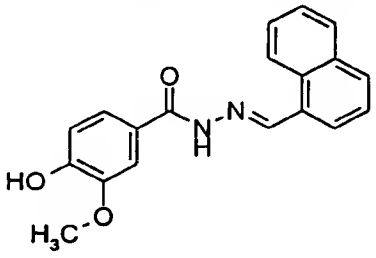
3,4-Dihydroxybenzoic acid (1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.64 (d, J = 8.6 Hz, 1 H), 7.13 (d, J = 8.2 Hz, 1 H), 7.19 (d, J = 2.0 Hz, 1 H), 7.36 - 7.42 (m, 3 H), 7.68 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 2 H), 8.65 (d, J = 8.2 Hz, 1 H), 8.88 (s, 1 H), 9.07 (s, 1 H), 9.46 (s, 1H), 11.45 (s, 1 H). MS (APCI): 307.

EXAMPLE 20:

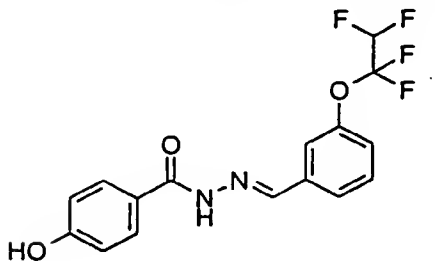
4-Hydroxy-3-methoxybenzoic acid (1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$) δ 3.94 (s, 3H), 6.74 (d, 1H), 7.37-7.52 (m, 6H), 7.77 (d, 1H), 7.89 (d, 2H), 8.67 (d, 1H), 9.93 (s, 1H), 10.90 (s, 1H). MS (APCI): 321.

EXAMPLE 23:

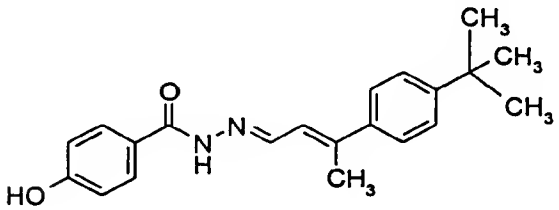
4-Hydroxybenzoic acid [3-(1,1,2,2-tetrafluoroethoxy)benzylidene]hydrazide



^{1}H NMR (DMSO-d$_6$) δ 6.49-6.78 (m, 3H), 7.10 (d, 1H), 7.32 (t, 1H), 7.41 (m, 2H), 7.57 (d, 2H), 8.23 (s, 1H), 10.01 (s, 1H), 11.59 (s, 1H). MS (APCI): 357.

EXAMPLE 24:

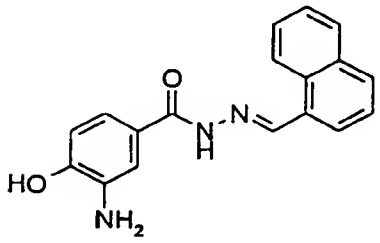
4-Hydroxybenzoic acid [3-(4-tert-butylphenyl)but-2-enylidene]hydrazide



^{1}H NMR (DMSO-d$_6$) δ 1.15 (s, 9H), 1.99 (s, 3H), 6.64 (s, 1H), 6.17 (d, 2H), 7.29 (s, 4H), 7.64 (d, 2H), 8.06 (s, 1H), 9.98 (s, 1H), 11.36 (s, 1H). MS (APCI): 337.

EXAMPLE 27:

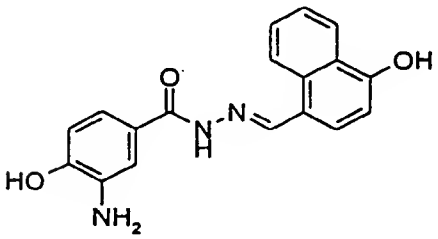
3-Amino-4-hydroxybenzoic acid (1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 4.71 (bs, 2 H), 6.68 (d, J = 8.1 Hz, 1 H), 7.01 (dd, J = 2.0, 8.2 Hz, 1 H), 7.17 (d, J = 2.0 Hz, 1 H), 7.51 - 7.62 (m, 3 H), 7.84 (d, J = 7.2 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 2 H), 8.75 (d, J = 7.6 Hz, 1 H), 9.01 (s, 1 H), 9.70 (s, 1 H), 11.54 (s, 1 H). MS (APCI): 306.

EXAMPLE 28:

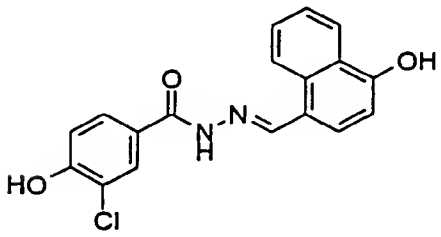
3-Amino-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 4.68 (bs, 2 H), 6.67 (d, J = 8.2 Hz, 1 H), 6.91 (d, J = 7.3 Hz, 1 H), 7.03 (d, J = 8.2 Hz, 1 H), 7.15 (s, 1 H), 7.43 - 7.65 (m, 3 H), 8.16 (d, J = 8.2 Hz, 1 H), 8.83 (m, 2 H), 10.71 (s, 1 H), 11.34 (s, 1 H). MS (APCI): 322.

EXAMPLE 31:

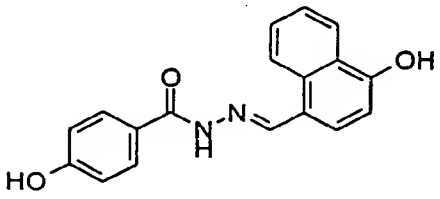
3-Chloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.90 (d, J = 8.0 Hz, 1 H), 7.02 (d, J = 8.5 Hz, 1 H), 7.50 (dd, J = J' = 7.8 Hz, 1 H), 7.58 (dd, J = 7.1, 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.93 (s, 1 H), 8.17 (d, J = 8.2 Hz, 1 H), 8.83 (s, 1 H), 8.88 (d, J =8.5 Hz, 1 H), 10.73 (s, 1 H), 10.88 (s, 1 H), 11.54 (s, 1 H). MS (APCI): 343, 341.

EXAMPLE 32:

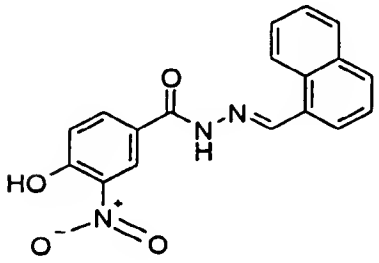
4-Hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.88 (d, 2 H), 6.98 (d, 1 H), 7.55 (dd, 1 H), 7.64 (dd, 1 H), 7.71 (d, 1 H), 7.82 (d, 2 H), 8.22 (d, 1 H), 8.94 (m, 2 H), 10.11 (s, 1 H), 10.77 (s, 1 H). MS (APCI): 307.

EXAMPLE 36:

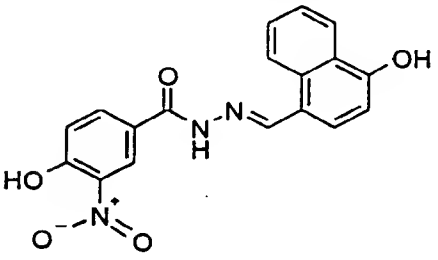
4-Hydroxy-3-nitrobenzoic acid (1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.15 (d, J = 9.3 Hz, 1 H), 7.37 - 7.48 (m, 4 H), 6.70 (d, J = 7.1 Hz, 1 H), 7.78 - 7.82 (m, 2 H), 8.29 (s, 1 H), 8.43 (d, J = 8.5 Hz, 1 H), 8.85 (s, 1 H).

EXAMPLE 37:

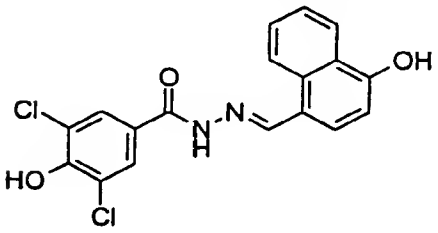
4-Hydroxy-3-nitrobenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.24 (d, J = 9.3 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 7.37 -7.52 (m, 3 H), 7.57 (d, J = 8.0 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H), 8.34 (s, 1 H), 8.76 (s, 1 H), 8.79 (s, 1 H), 10.57 (s, 1 H), 11.17 (m, 1 H).

EXAMPLE 40:

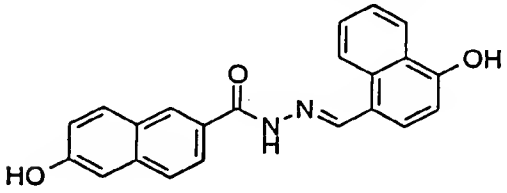
3,5-Dichloro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.98 (d, 1 H), 7.58 (dd, 1 H), 7.68 (dd, 1 H), 7.78 (d, 1 H), 8.02 (s, 2 H), 8.27 (d, 1 H), 8.90 (s, 1 H), 8.96 (d, 1 H), 10.81 (s, 1 H), 10.98 (s, 1 H), 11.67 (s, 1 H). MS (APCI): 375, 377.

EXAMPLE 41:

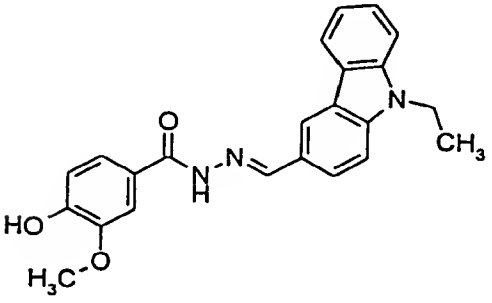
6-Hydroxy-2-naphthoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

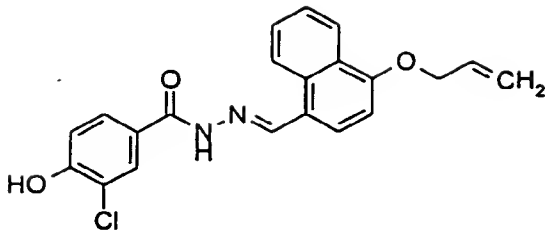


^{1}H NMR (DMSO-d$_6$): δ 6.04 (d, 2 H), 6.33 (m, 1 H), 6.62 (dd, 2 H), 6.79 (dd, 2 H), 7.06 (d, 2 H), 7.44 (d, 2 H), 8.27 (d, 2 H), 8.39 (s, 2 H).

EXAMPLE 42:

4-Hydroxy-3-methoxybenzoic acid (9-ethyl-9H-3-carbazolylmethylene)hydrazide

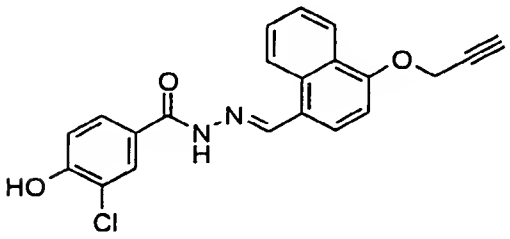




^{1}H NMR (DMSO-d_6): δ 4.68 (m, 2 H), 5.21 (d, 1 H), 5.38 (d, 1 H), 5.90 -6.10 (m, 1 H), 6.86 (dd, 2 H), 7.42 (dd, 1 H), 7.53 (dd, 1 H), 7.67 (dd, 2 H), 7.86 (s, 1 H), 8.18 (d, 1 H), 8.78 (s, 1 H), 8.82 (d, 1 H), 10.9 (s, 1 H), 12.0 (s, 1 H). MS (APCI): 381.

EXAMPLE 46:

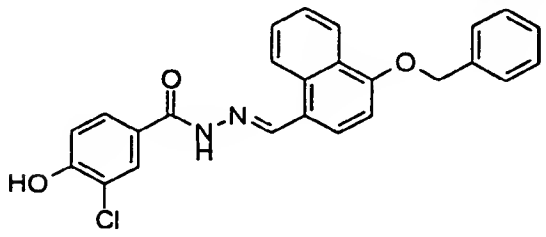
3-Chloro-4-hydroxybenzoic acid (4-ethynylmethoxy-1-naphthylmethylene)hydrazide

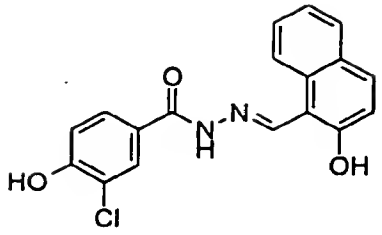


^{1}H NMR (DMSO-d_6): δ 3.60 (s, 1 H), 5.06 (s, 2 H), 6.99 (d, 1 H), 7.12 (d, 1 H), 7.55 (t, 1 H), 7.66 (t, 1 H), 7.73 (t, 1 H), 7.93 (s, 1 H), 8.02 (d, 1 H), 8.16 (t, 1 H), 8.86 (d, 1 H), 9.27 (d, 1 H), 10.90 (s, 1 H), 11.62 (s, 1 H). MS (APCI): 378.

EXAMPLE 47:

3-Chloro-4-hydroxybenzoic acid (4-benzyloxy-1-naphthylmethylene)hydrazide

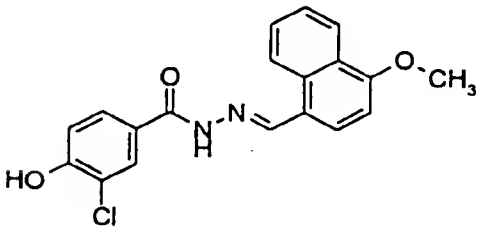




^{1}H NMR (DMSO-d$_6$): δ 6.98 (d, 1 H), 7.98 (d, 1 H), 7.29 (dd, 1 H), 7.48 (dd, 1 H), 7.69 (d, 1 H), 7.78 (dd, 2 H), 7.90 (s, 1 H), 8.06 (d, 1 H), 9.32 (s, 1 H), 11.00 (s, 1 H). MS (APCI): 341.

EXAMPLE 51:

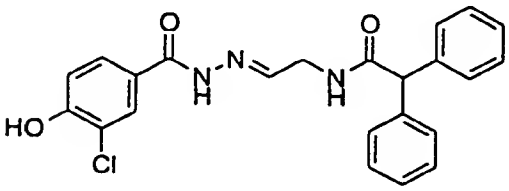
3-Chloro-4-hydroxybenzoic acid (4-methoxy-1-naphthylmethylene)hydrazide

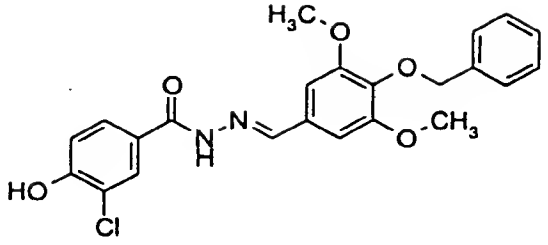


^{1}H NMR (DMSO-d$_6$): δ 4.05 (s, 3 H), 7.06 (m, 2 H), 7.59 (dd, 1 H), 7.70 (dd, 1 H), 7.81 (d, 1 H), 7.86 (d, 1 H), 8.00 (s, 1 H), 8.27 (d, 1 H), 8.93 (s, 1 H), 8.99 (d, 1 H), 11.00 (s, 1 H). MS (APCI): 341, 339.

EXAMPLE 52:

N-(2-[(3-Chloro-4-hydroxybenzoyl)hydrazono]ethyl)-2,2-diphenylacetamide

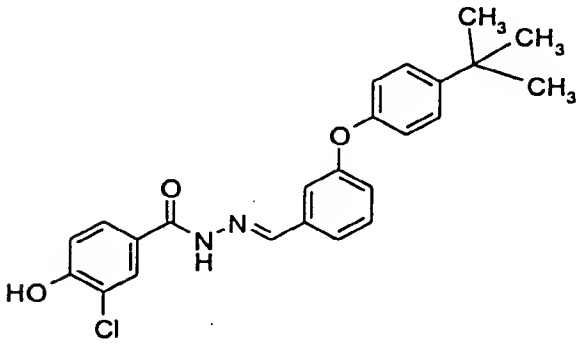




^{1}H NMR (DMSO-d$_6$): δ 3.86 (s, 6 H), 4.98 (s, 2 H), 7.03 (s, 2 H), 7.09 (d, 1 H), 7.25 - 7.33 (m, 3 H), 7.48 (m, 2 H), 7.89 (dd, 1 H), 7.99 (s, 1 H), 8.32 (s, 1 H), 11.00 (s, 1 H). MS (APCI): 441.

EXAMPLE 56:

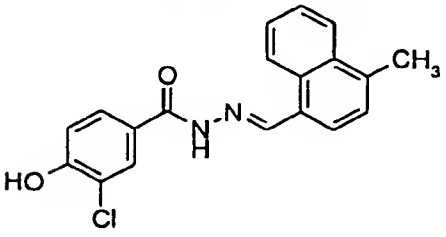
3-Chloro-4-hydroxybenzioc acid [3-(4-tert-butylphenoxy)benzylidene]hydrazide



^{1}H NMR (DMSO-d$_6$): δ 1.05 (s, 9 H), 6.90 (m, 3 H), 7.09 (d, 1 H), 7.30 (t, 1 H), 7.40 (m, 3 H), 7.69 (m, 2 H), 7.88 (s, 1 H), 8.44 (s, 1 H), 10.60 (s, 1 H), 11.55 (s, 1 H). MS (APCI): 423.

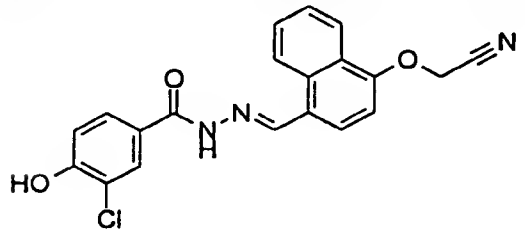
EXAMPLE 57:

3-Chloro-4-hydroxybenzoic acid (4-methyl-1-naphthylmethylene)hydrazide



EXAMPLE 60:

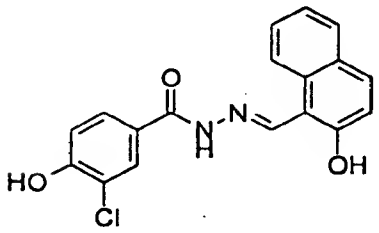
3-Chloro-4-hydroxybenzoic acid (4-cyanomethoxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 5.40 (s, 2 H), 7.00 (d, 1 H), 7.21 (d, 1 H), 7.58 - 7.80 (m, 3 H), 7.82 (d, 1 H), 7.96 (s, 1 H), 8.18 (d, 1 H), 8.90 (s, 2 H), 9.28 (s, 1 H), 11.62 (s, 1 H). MS (APCI): 380, 382.

EXAMPLE 61:

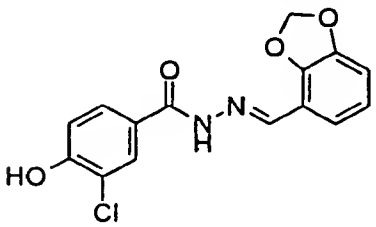
3-Chloro-4-hydroxybenzoic acid (2-hydroxy-1-naphthylmethylene)hydrazide

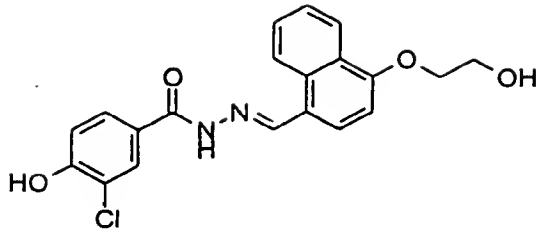


^{1}H NMR (DMSO-d$_6$): δ 7.18 (d, 1 H), 7.30 (d, 1 H), 7.50 (dd, 1H), 7.68 (dd, 1 H), 7.88 (d, 1 H), 7.95 (m, 2 H), 8.08 (s, 1 H), 8.29 (d, 1 H), 9.51 (s, 1 H), 11.12 (s, 1 H), 12.12 (s, 1 H). MS (APCI): 341, 343.

EXAMPLE 62:

3-Chloro-4-hydroxybenzoic acid (2,3-methylenedioxybenzylidene)hydrazide

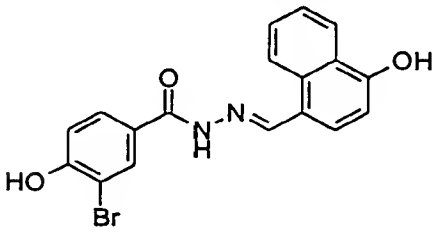




^{1}H NMR (DMSO-d$_6$): δ 3.81 (t, J = 4.8 Hz, 2 H), 4.16 (t, J = 4.8 Hz, 2 H), 6.46 (d, J = 8.5 Hz, 1 H), 7.01 (d, J = 8.5 Hz, 1 H), 7.51 - 7.61 (m, 3 H), 7.72 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 2.1 Hz, 1 H), 8.30 (d, J = 8.2 Hz, 1 H), 8.85 (s, 1 H), 8.87 (d, J = 8.5 Hz, 1 H), 11.38 (s, 1 H). MS (APCI): 385, 387.

EXAMPLE 66:

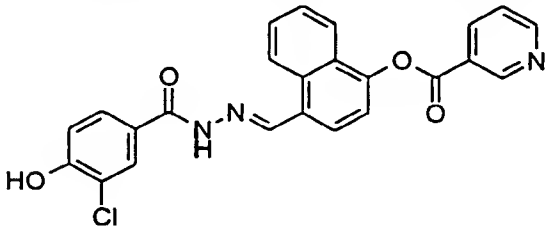
3-Bromo-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide



^{1}H NMR (DMSO-d$_6$): δ 6.90 (d, J = 8.0 Hz, 1 H), 7.00 (d, J = 8.0 Hz, 1 H), 7.47 (dd, J = J' = 8.0 Hz, 1 H), 7.58 (dd, J = J " = 8.0 Hz, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.77 (dd, J = 2.0, 8.0 Hz, 1 H), 8.08 (d, J = 2.0 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.83 (s, 1 H), 8.88 (d, J = 8.0 Hz, 1 H), 10.73 (s, 1 H), 11.53 (s, 1 H). MS (APCI): 385, 387.

EXAMPLE 67:

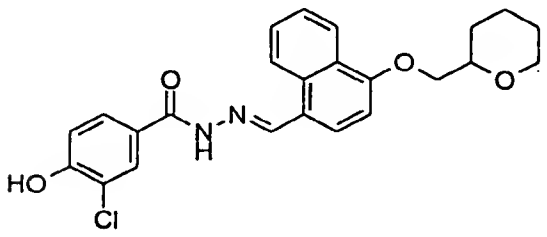
Nicotinic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyl ester



= 7.4 Hz, 1 H), 7.62 (dd, J = J ' = 7.5 Hz, 1 H), 7.72 -7.93 (m, 2 H), 7.94 (d, J = 2.1 Hz, 1 H), 8.22 (d, J = 8.0 Hz, 1 H), 8.87 (s, 1 H), 8.90 (d, J = 8.5 Hz, 1 H), 10.94 (s, 1 H), 11.60 (s, 1 H). MS (APCI): 437, 439.

EXAMPLE 70:

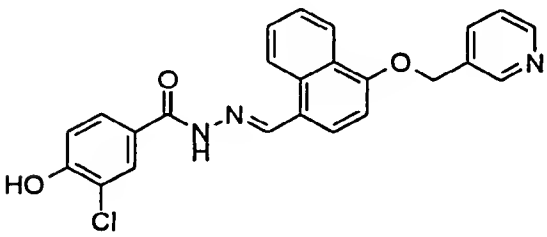
3-Chloro-4-hydroxybenzoic acid [4-(tetrahydro-2-pyranylmethoxy)-1-naphthylmethylene]-hydrazide



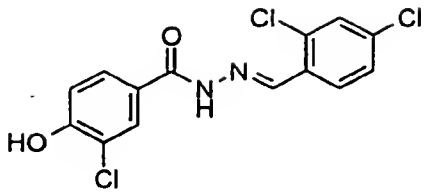
^{1}H NMR (DMSO-d$_6$): δ 1.35 (m, 3 H), 1.60 - 1.71 (m, 2 H), 3.15 - 3.38 (m, 2 H), 3.64 (m, 1 H), 3.78 (m, 1 H), 4.02 (m, 2 H), 6.94 (d, J = 8.5 Hz, 2 H), 7.46 (dd, J = J' = 7.4 Hz, 1 H), 7.54 (dd, J = J ' = 8.2 Hz, 1 H), 7.66 (m, 2 H), 7.86 (d, J = 2.1 Hz, 1 H), 8.13 (d, J = 8.0 Hz, 1 H), 8.78 (s, 1 H), 8.83 (d, J = 8.5 Hz, 1 H), 10.83 (s, 1 H), 11.52 (s, 1 H). MS (APCI): 439, 441.

EXAMPLE 71:

3-Chloro-4-hydroxybenzoic acid [4-(3-pyridylmethoxy)-1-naphthylmethylene]hydrazide



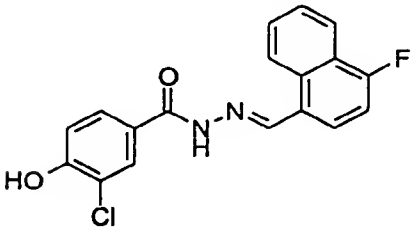
^{1}H NMR (DMSO-d$_6$): δ 5.28 (m, 2 H), 6.94 (d, J = 8.5 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 7.34 (dd, J = 4.8, 7.8 Hz, 1 H), 7.45 (dd, J = J' = 7.6 Hz, 1 H), 7.54 (dd, J = J ' = 7.5 Hz, 1 H), 7.66 (d, J = 8.5 Hz, 1 H), 7.70 (d, J = 8.2 Hz, 1 H), 7.86 (m, 2 H), 8.15 (d, J = 8.0 Hz, 1 H),



^{1}H NMR (DMSO-d$_6$): δ 7.02 (d, J = 8.5 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.66 (s, 1 H), 7.73 (d, J = 8.2 Hz, 1 H), 7.95 (m, 2 H), 8.71 (s, 1 H), 11.97 (s, 1 H), 11.94 (s, 1 H). MS (APCI): 345.

EXAMPLE 75:

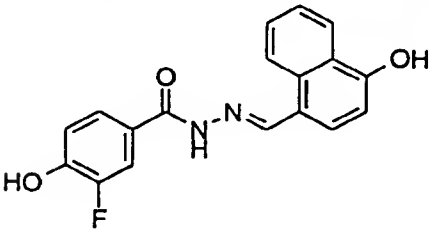
3-Chloro-4-hydroxybenzoic acid (4-fluoro-1-naphthylmethylene)hydrazide

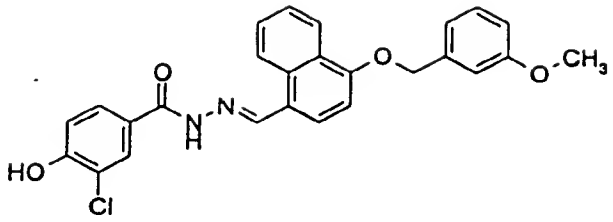


^{1}H NMR (DMSO-d$_6$): δ 7.00 (d, J = 8.5 Hz, 1 H), 7.33 (dd, J = 8.2, 10.3 Hz, 1 H), 7.62 - 7.72 (m, 3 H), 7.82 (m, 1 H), 7.91 (d, J = 1.9 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H), 8.09 (m, 1 H), 8.91 (s, 1 H), 10.81 (s, 1 H), 11.67 (s, 1 H). MS (APCI): 343.

EXAMPLE 76:

3-Fluoro-4-hydroxybenzoic acid (4-hydroxy-1-naphthylmethylene)hydrazide

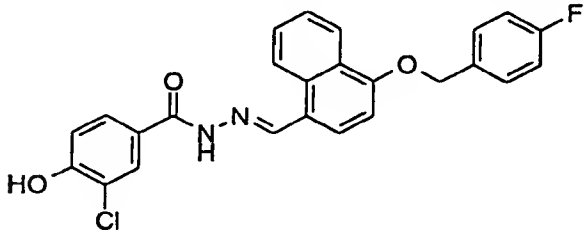




^{1}H NMR (DMSO-d$_6$): δ 3.71 (s, 3 H), 5.29 (s, 2 H), 6.87 (d, J = 8.5 Hz, 1 H), 7.00 - 7.14 (m, 4 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.55 (m, 1 H), 7.68 (m, 1 H), 7.75 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.87 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 11.00 (s, 1 H), 11.62 (s, 1 H). MS (APCI): 461.

EXAMPLE 80:

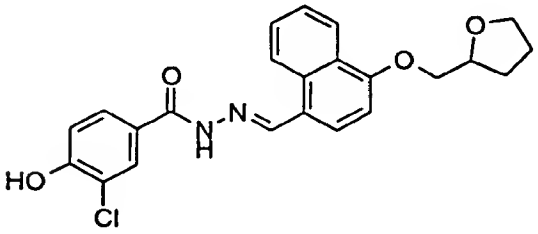
3-Chloro-4-hydroxybenzoic acid [4-(4-fluorobenzyloxy)-1-naphthylmethylene]hydrazide



^{1}H NMR (DMSO-d$_6$): δ 5.30 (s, 2 H), 7.02 (d, J = 8.5 Hz, 1 H), 7.13 - 7.25 (m, 3 H), 7.53 - 7.60 (m, 4 H), 7.79 (m, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.23 (d, J = 8.0 Hz, 1 H), 8.88 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 10.93 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 449, 451.

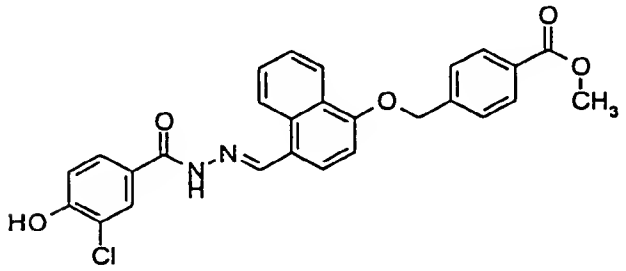
EXAMPLE 81:

3-Chloro-4-hydroxybenzoic acid [4-(2-tetrahydrofuranylmethoxy)-1-naphthylmethylene]-hydrazide



EXAMPLE 84:

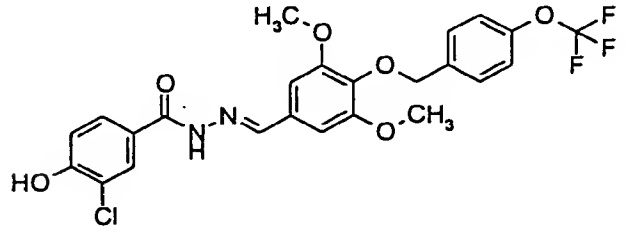
4-(4-[3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-1-naphthyloxymethyl)benzoic acid methyl ester



^{1}H NMR (DMSO-d$_6$): δ 3.80 (s, 3 H), 5.43 (s, 2 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 1 H), 7.54 (m, 1 H), 7.57 (d, J = 8.0 Hz, 4 H), 7.93 - 7.99 (m, 3 H), 8.30 (d, J = 8.0 Hz, 1 H), 8.87 (s, 1 H), 8.93 (d, J = 8.5 Hz, 1 H), 10.91 (s, 1 H), 11.63 (s, 1 H). MS (APCI): 489, 491.

EXAMPLE 85:

3-Chloro-4-hydroxybenzoic acid [3,5-dimethoxy-4-(4-trifluoromethoxybenzyloxy)benzylidene]hydrazide



^{1}H NMR (DMSO-d$_6$): δ 3.76 (s, 6 H), 4.91 (s, 2 H), 6.95 - 7.00 (m, 3 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.68 (d, J = 2.0, 8.5 Hz, 1 H), 7.88 (s, 1 H), 8.29 (s, 1 H), 10.91 (s, 1 H), 11.69 (s, 1 H). MS (APCI): 525, 527.

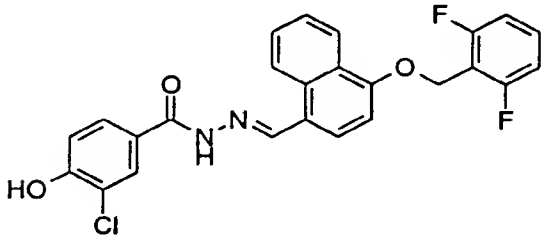
EXAMPLE 86:

3-Chloro-4-hydroxybenzoic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]-hydrazide

^{1}H NMR (DMSO-d$_6$): δ 5.36 (s, 2 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.19 - 7.28 (m, 3 H), 7.39 (m, 1 H), 7.53 (m, 1 H), 7.63 (m, 2 H), 7.72 - 7.80 (m, 2 H), 7.94 (d, J = 2.1 Hz, 1 H), 8.19 (d, J = 8.3 Hz, 1 H), 8.88 (s, 1 H), 8.92 (d, J = 8.5 Hz, 1 H), 10.90 (s, 1 H), 11.64 (s, 1 H). MS (APCI): 449, 451.

EXAMPLE 89:

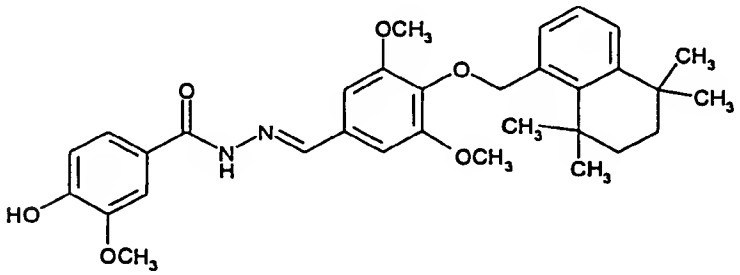
3-Chloro-4-hydroxybenzoic acid [4-(2,6-difluorobenzyloxy)-1-naphthylmethylene]hydrazide



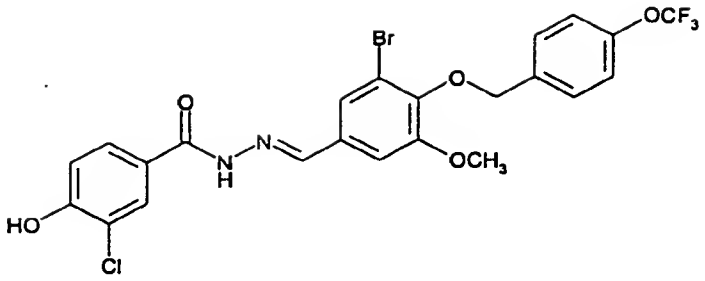
^{1}H NMR (DMSO-d$_6$): δ 5.34 (s, 2 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.16 (d, J = 8.2 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.51 (m, 2 H), 7.72 (m, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.94 (d, J = 2.1 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 1 H), 8.89 (s, 1 H), 8.91 (d, J = 8.5 Hz, 1 H), 10.97 (s, 1 H), 11.65 (s, 1 H). MS (APCI): 467, 469.

EXAMPLE 90:

4-Hydroxy-3-methoxybenzoic acid [3,5-dimethoxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-1-ylmethoxy)benzylidene]hydrazide



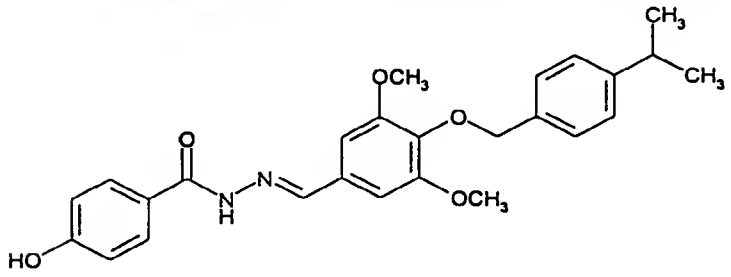
^{1}H NMR (DMSO-d$_6$): δ 1.2 (s, 12H), 1.63 (s, 4H), 3.82 (s, 6H), 3.85 (s, 3H), 4.90 (s, 2H), 6.88 (d, 1H), 7.01 (s, 2H), 7.18 (d, 1H), 7.29 (d, 1H), 7.38 (s, 1H), 7.44 (d, 1H), 7.48 (s, 1H), 8.40 (brd s, 1H), 11.62 (s 1H); MS (APCI): 547.1.



^{1}H NMR (DMSO-d$_6$): δ 3.92 (s, 3H), 5.07 (s, 2H), 7.07 (d, 1H), 7.40 (m, 3H), 7.52 (s, 1H), 7.63 (d, 2H), 7.77 (dd, 1H), 7.97 (d, 1H), 8.35 (s, 1H), 11.00 (brd s, 1H), 11.86 (s, 1H); MS (FAB): 575.0

EXAMPLE 94:

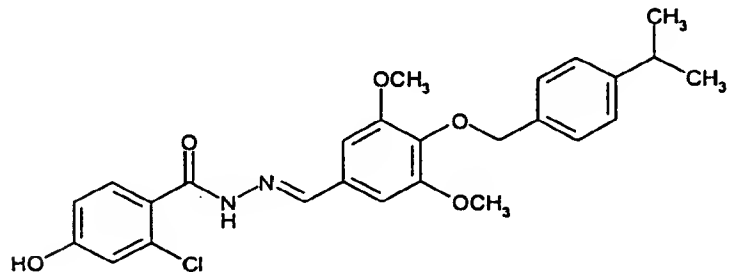
4-Hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]hydrazide



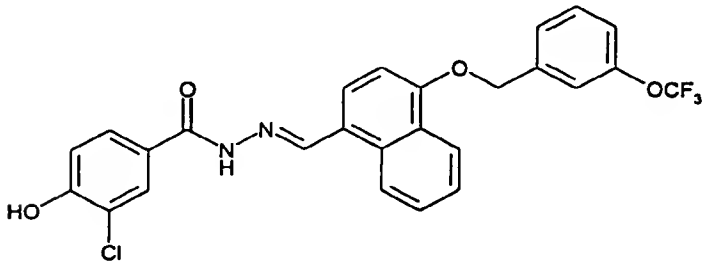
^{1}H NMR (DMSO-d$_6$): δ 1.05 (d, 6H), 2.71 (m, 1H), 3.67 (s, 6H), 4.75 (s, 2H), 6.70 (d, 2H), 6.85 (s, 2H), 7.14 (d, 2H), 7.21 (d, 2H), 7.64 (d, 2H), 8.21 (brd s, 1H), 9.97 (brd s, 1H), 11.47 (s, 1H); MS (APCI): 448.9.

EXAMPLE 95:

2-Chloro-4-hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]hydrazide:



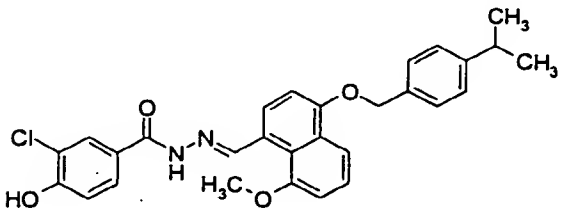
3-Chloro-4-hydroxybenzoic acid [4-(3-trifluoromethoxybenzyloxy)naphth-1-ylmethylene]hydrazide



^{1}H NMR (DMSO-d$_6$): δ 5.46 (s, 2H), 7.10 (d, 1H), 7.20 (d, 1H), 7.37 (d, 1H), 7.65 (m, 5H), 7.82 (m, 2H), 8.01 (s, 1H), 8.32 (d, 1H), 8.97 (m, 2H), 11.70 (s, 1H); MS (APCI): 514.8

EXAMPLE 99:

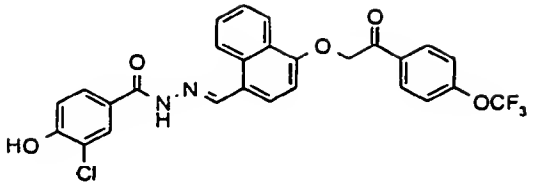
3-Chloro-4-hydroxy-benzoic acid [4-(4-isopropylbenzyloxy)-8-methoxynaphthalen-1-ylmethylene]-hydrazide



4-hydroxy-8-methoxynaphthalene-1-carbaldehyde (2 g, 9.9 mmol) was dissolved in DMF (25 mL). To this mixture potassium carbonate (6.8 g, 50 mmol) and 4-isopropylbenzylchloride (1.8 g, 10.4 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. Water (100 mL) was added and the resulting mixture was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried ($MgSO_4$) and evaporated in vacuo to afford 3.0 g crude product. This was purified using column chromatography on silica gel (300 mL) eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 2.57 g (81%) of 4-isopropylbenzyloxy-8-methoxynaphthalene-1-carbaldehyde.

Calculated for $C_{22}H_{22}O_3$:
C, 79.02%; H, 6.63%. Found:

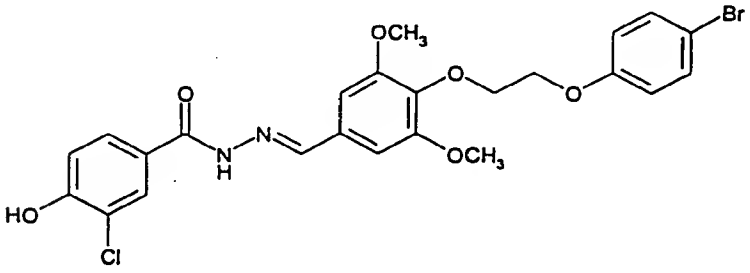
EXAMPLE 102:



^{1}H NMR (DMSO-d_6) δ 5.85 (s, 2H), 7.05 (t, 2H), 7.52-7.63 (m, 4H), 7.73 (m, 2H), 7.95 (s, 1H), 8.16 (d, 2H), 8.33 (d, 1H), 8.90 (s, 1H), 893 (s, 1H), 10.90 (brd s, 1H), 11.63 (s, 1H); MS (FAB): 543

EXAMPLE 103:

3-Chloro-4-hydroxybenzoic acid {4-[2-(4-bromophenoxy)ethoxy]-3,5-dimethoxybenzylidene}hydrazide



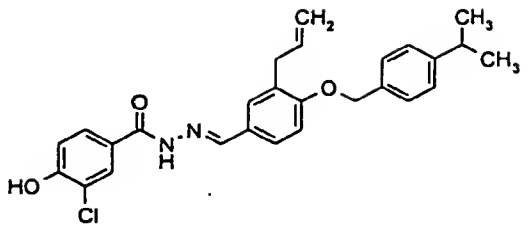
^{1}H NMR (DMSO-d_6): δ 3.78 (s, 6H), 4.21 (m, 4H), 6.87 (d, 2H), 7.00 (s, 2H), 7.05 (d, 1H), 7.44 (d, 2H), 7.75 (dd, 1H), 7.96 (s, 1H), 8.36 (s, 1H), 10.95 (brd s, 1H), 11.66 (s, 1H); MS(APCI): 548.8.

EXAMPLE 104:

3-Chloro-4-hydroxybenzoic acid [4-(3-methoxy-3-(4-methylphenyl)-propyloxy)naphth-1-ylmethylene]hydrazide

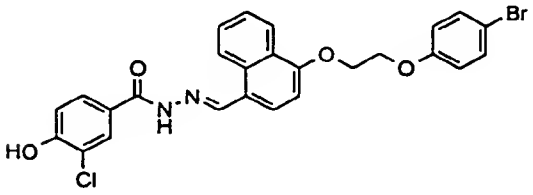
^{1}H NMR (DMSO-d_6) : δ 1.13 (d, 6H), 2.80 (m, 1H), 3.20 (m, 2H), 3.85 (s, 3H), 4.82 (s, 2H), 5.00 (d, 2H), 5.70 (m, 1H), 6.96 (s, 1H), 7.05 (s, 1H), 7.20 (d, 2H), 7.30 (d, 2H), 7.70 (d, 1H), 7.89 (s, 1H), 8.28 (s, 1H), 10.80 (brd s, 1H), 11.61 (s, 1H); MS (APCI): 493.1.

EXAMPLE 110:



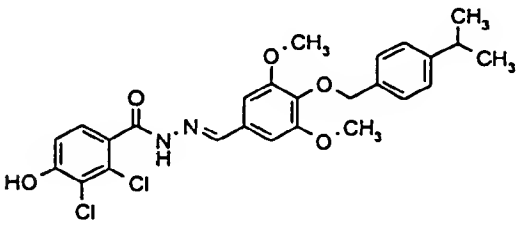
^{1}H NMR (DMSO-D_6): δ 1.1 (d, 6H), 2.8 (septet, 1H), 3.3 (d, 1H), 5.0 (d, 1H), 5.1 (d, 1H), 5.2 (s, 2H), 5.9 (m, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2 (d, 2H), 7.3 (d, 2H), 7.4 (d, 1H), 7.5 (s, 1H), 7.7 (dd, 1H), 7.9 (d, 1H), 8.3 (s, 1H), 10.9 (brd s, 1H), 11.5 (s, 1H); MS (APCI): 463.5, 465.1.

EXAMPLE 111:



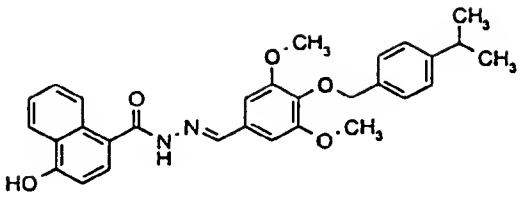
^{1}H NMR (DMSO-D_6): δ 4.47 (t, 2H), 4.54 (t, 2H), 7.01 (d, 2H), 7.07 (d, 1H), 7.14 (d, 1H), 7.45 (d, 2H), 7.53 (t, 1H), 7.27 (d, 1H), 7.79 (m, 2H), 7.96 (d, 1H), 8.17 (d, 1H), 8.91 (s, 1H), 8.94 (d, 1H), 10.92 (s, 1H), 11.64 (s, 1H), MS (APCI): 539.3, 541.1, 543.1.

EXAMPLE 112:



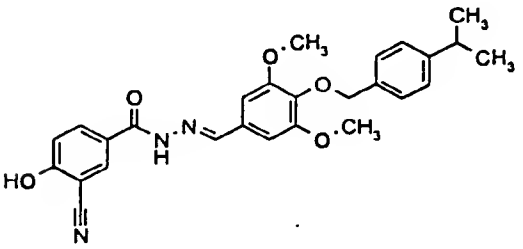
^{1}H NMR (DMSO-D_6): δ 1.18 (d, 6H), 2.87 (septet, 1H), [3.67 (s, 1.5H) + 3.81 (s, 4.5H), 6H], [4.83 (s, 0.5H) + 4.90 (s, 1.5H), 2H], 6.73 (s, 0.5H) + [7.02 (m, 2.5H), + 7.27 (m, 2.5H) + 7.37 (m, 2.5H), 8H], [7.92 (s, 0.3H) + 8.17 (s, 0.7H), 1H], [10.96 (s, 0.3H) + 11.12 (s, 0.7H), 1H], [11.82 (s, 0.7H) + 11.95 (s, 0.3H), 1H]; MS (APCI): 517.6, 519.2.

EXAMPLE 116:



^{1}H NMR (DMSO-D_6): δ 1.19 (d, 6H), 2.88 (septet, 1H), 3.83 (s, 6H), 4.90 (s, 2H), 6.87 (d, 1H), 7.03 (s, 2H), 7.23 (d, 2H), 7.36 (d, 2H), 7.53 (m, 3h), 8.26 (m, 3H), 10.73 (s, 1H), 11.82 (s, 1H); MS (APCI): 499.8.

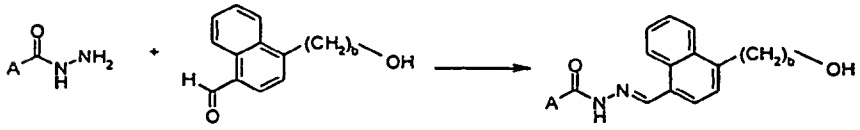
EXAMPLE 117:



^{1}H NMR (DMSO-D_6): δ 1.20 (d, J = 6.9, 6H), 2.89 (sept, J = 6.9, 1H), 3.84 (s, 6H), 4.91 (s, 2H), 7.03 (br s, 2H), 7.12 (d, J = 8.8, 1H), 7.23 (d, J = 8.0, 2H), 7.37 (d, J = 8.0, 2H), 8.04 (dd, J = 2.2, 8.8, 1H), 8.21 (br s, 1H), 8.35 (br s, 1H), 11.78 (s, 1H), 11.89 (br s, 1H); MS (APCI, neg): 472.

Preparation of acyl-hydrazones of 4-(2-hydroxyethyl)-1-naphthaldehyde:

<u>General procedure for synthesis of compounds of the general formula X:</u>



formula X

7.61 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 8.09 - 8.12 (m, 1H), 8.29 (dd, J = 2.5, 7.1 Hz, 1H). GCMS (pos), 334, 336.

1-Formyl-4-(2-tetrahydropyranyloxyethyl)naphthalene:

A solution of 1-bromo-4-(2-tetrahydropyranyloxyethyl)naphthalene in anhydrous THF (15 mL) under nitrogen was cooled to -78°C. n-Butyl lithium (1.4 mL of a 2.5 M solution in hexane) was added via syringe, and the mixture was stirred at the same temperature for 30 min. DMF (1.1 mL) was added, and the mixture was allowed to reach room temperature. It was diluted with satd. NH_4Cl solution (10 mL), extracted with ether (3 x 10 ml), dried ($MgSO_4$) and concentrated. Flash chromatography using hexane/ethyl acetate 5:1 as eluent provided 408 mg (54%) of a colorless oil.

^{1}H NMR ($CDCl_3$) δ = 1.48 -1.69 m (6H), 3.45 - 3.50 (m, 3H), 3.69 - 3.85 (m, 2H), 4.07 - 4.17 (m, 1H), 4.61 (m, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.62 -7.73 (m, 2H), 7.92 (d, J = 7.3 Hz, 1H), 8.20 (d, J = 1.0, 8.1 Hz, 1H), 10.36 (s, 1H). GCMS: 284

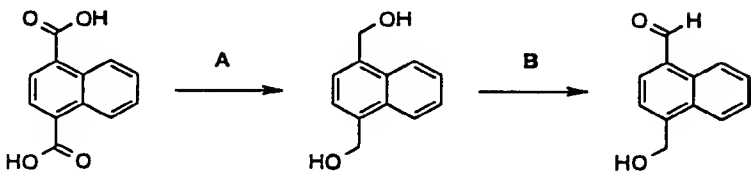
1-Formyl-4-(2-hydroxyethyl)naphthalene:

1-Formyl-4-(2-tetrahydropyranyloxyethyl)naphthalene (400 mg, 1.40 mmol) was dissolved in methanol (15 mL), and p-toluene sulfonic acid (45 mg) was added. The mixture was stirred at room temperature for 16 h, and concentrated. The residue was dissolved in ethyl acetate (3 x 10 mL), washed with satd. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography using hexane/ethyl acetate 3:1 as eluent provided 182 mg (65%) of a colorless oil .

^{1}H NMR ($CDCl_3$) δ = 2.09 (s, 1H), 3.40 (t, J = 6.6 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.61- 7.71 (m, 2H), 7.88 (d, J =7.3 Hz, 1H), 8.13 (dd, J = 1.3, 8.0 Hz, 1H), 9.29 (dd, J = 1.3, 8.0 Hz, 1H), 10.28 (s, 1H). GCMS: 200

The following compounds were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 1-formyl-4-(2-hydroxyethyl) naphthalene (from step D) with 4-hydroxy benzoic acid hydrazides.

Preparation of acylhydrazones of 4-hydroxymethylnaphthaldehyde:



Step A:

The 1,4-Naphthalenedicarboxylic acid (25 g, 116 mmol) was dripped into a mixture of Lithium Aluminum Hydride (15 g, 395 mmol) in 600 mL of anhydrous THF and refluxed for two days. The mixture was cooled in an ice bath and excess LAH was decomposed by the slow addition of methanol followed by ice chips. THF was removed under vacuum and the residue was acidified with 1N HCl. The product was extracted with ethyl acetate (3x), washed with aqueous sodium bicarbonate (3x), water, brine, and dried over magnesium sulfate. 1,4-Bishydroxymethylnaphthalene (70%) was obtained as a solid after evaporation of the solvent and can be used in the subsequent oxidation step without further purification. A portion of the material was purified by column chromatography using hexane/ethyl acetate (80/20 to 75/25) for characterization purposes.

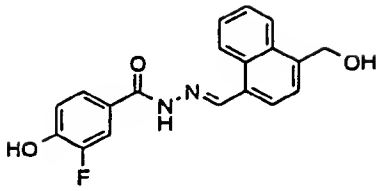
^{1}H NMR (DMSO-D6): δ 5.19 (s, 4H), 7.77 (m, 4H), 8.32 (m, 2H).

Step B:

To a solution of 1,4-bishydroxymethylnaphthalene (12 g, 65 mmol) in ethyl acetate (300 ml) was added manganese dioxide (28 g, 325 mmol). After stirring for 45 minutes most of the starting material had disappeared and two new spots (mono aldehyde and dialdehyde) were seen on TLC. The upper spot corresponds to the dialdehyde. The mixture was passed through a bed of Celite and eluted with additional volumes of ethyl acetate. The solvent was evaporated and 4-hydroxymethylnaphthaldehyde was purified by column chromatography using hexane/ethyl acetate (80/20 to 75/25) in 50% yield.

H NMR (DMSO-D6): δ 5.19 (s, 2H), 5.71 (brd s, 1H), 7.73 (t, 1H), 7.78 (t, 1H), 7.95 (d, 1H), 8.26 (m, 2H), 9.34 (d, 1H), 10.46 (s, 1H).

EXAMPLE 122:



The above compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above aldehyde with 3-fluoro-4-hydroxybenzoic acid hydrazide.

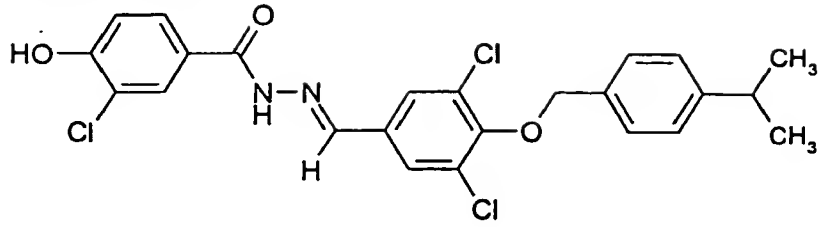
^{1}H NMR (DMSO-D_6): d4.84 (s, 2H), 6.91 (t, 1H), 7.43-7.53 (m, 4H), 7.62 (d, 1H), 7.72 (d, 1H), 7.96 (d, 1H), 8.68 (d, 1H), 8.98 (s, 1H), 11.71 (brd s, 1H); MS (APCI): 339.4, 340.3.

The compounds of formula II can also be prepared by parallel synthesis using the protocol mentioned above in a combinatorial approach. Thousands of compounds of formula II can thus be prepared by this combinatorial approach which can be semi- or fully automated. The automation of this protocol can be performed using solution phase combinatorial chemistry in e.g. a 96 well setup using an automated synthesizer device. In the first step of the synthesis the aldehydes or ketones may be prepared according to Scheme II by a combination of a selected number of aldehydes or ketones with a selected number of alkylating reagents. In the second step the formed aldehydes/ketones can be combined with a selected number of the hydrazides (which may be synthesized according to Scheme I) thereby generating a predetermined very large number of compounds as single entities.

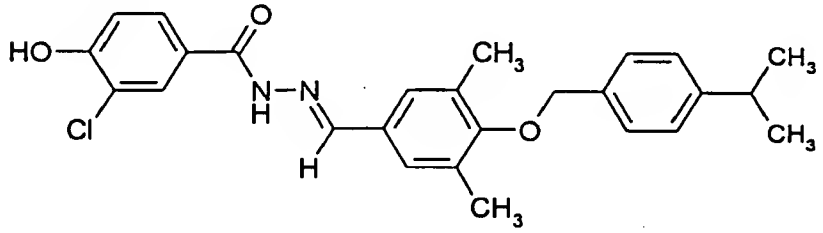
The synthesized compounds mentioned above are examples of such compounds that can be prepared using this combinatorial methodology.

By application of the above methodology, the following compounds may also be synthesized:

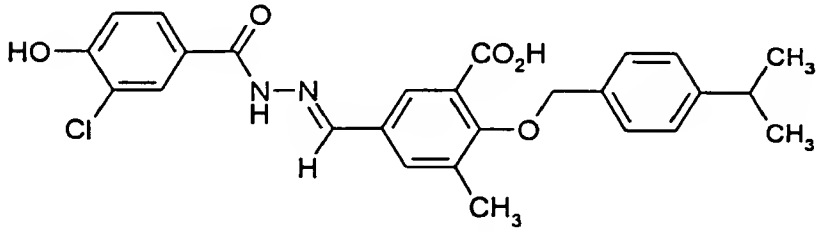
EXAMPLE 127:



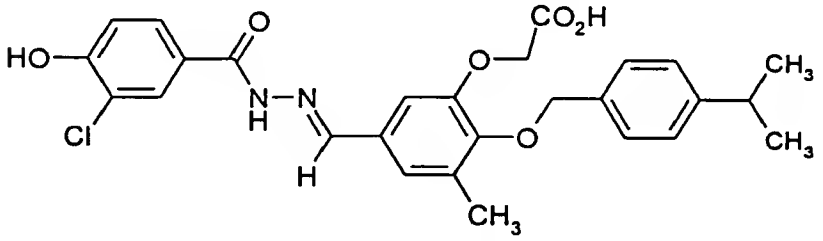
EXAMPLE 128:



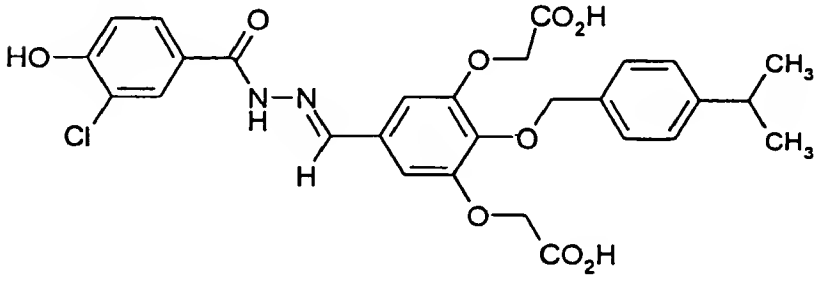
EXAMPLE 129:



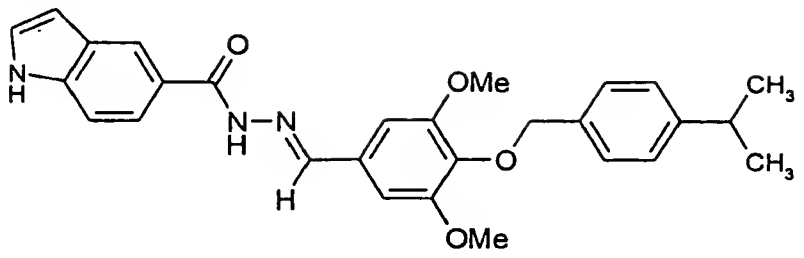
EXAMPLE 130:



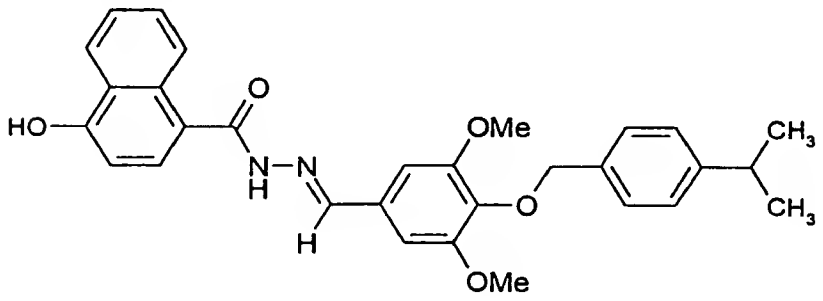
EXAMPLE 131:



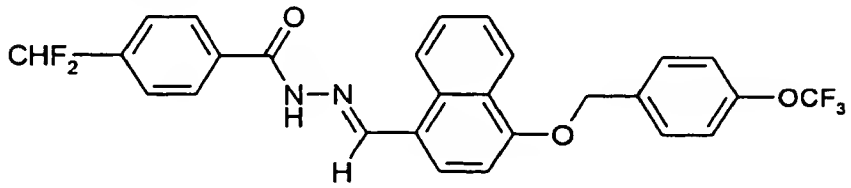
EXAMPLE 137:



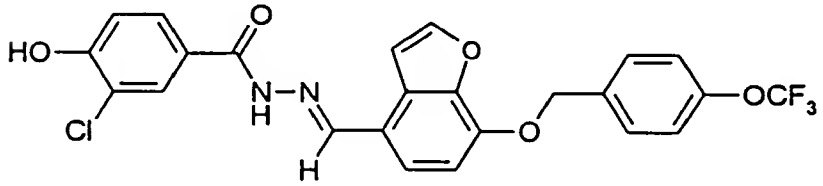
EXAMPLE 138:



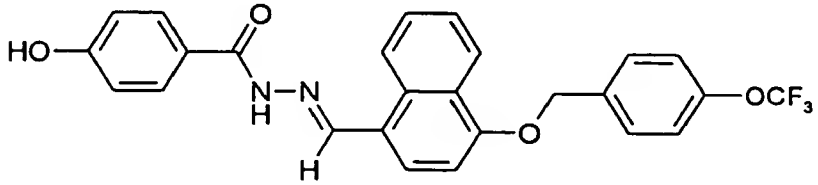
EXAMPLE 139:



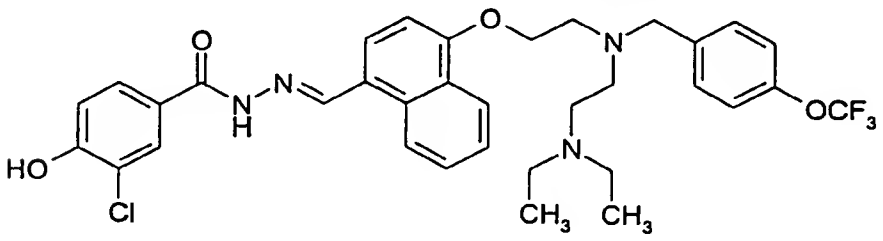
EXAMPLE 140:



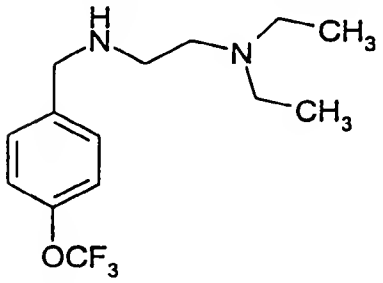
EXAMPLE 141:



3-Chloro-4-hydroxybenzoic acid {4-[2-[N'-(2-N,N-diethylaminoethyl)-N'-(4-trifluoromethoxy-benzylamino)]]ethoxy -1-naphthylmethylene}hydrazide



N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine:

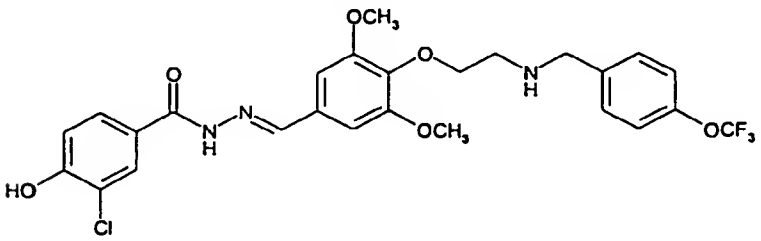


A solution of (4-trifluoromethoxy)benzaldehyde (1.9 g, 10 mmoles), N,N-diethylethylene-diamine (1.16 g, 10 mmoles), zinc chloride (1.36 g, 10 mmoles) and sodium cyanoborohydride (1.26 g, 20 mmoles) in methanol (10 mL) in a dry 100 mL round- bottom flask was stirred at room temperature for 8 hours. Water (20 mL) was then added and most of the methanol was removed in vacuo. The residue was distributed between ethyl acetate and 1N HCl. The acidic aqueous phase was basified with excess of sodium hydroxide. Crude N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine was obtained. The crude product was used in the following reaction without further purification.

MS (CI): 291. ^{1}H NMR ($CDCl_3$): δ 7.4 (m, 2H), 7.2 (m, 2H), 3.9 (bs, 2H), 3.1-2.6 (m, 9H), 1.4-1.1 (t, 6H).

To a flask containing N,N-diethyl-N'-(4-trifluoromethoxybenzyl)ethylenediamine (0.29 g, 1 mmole) in DMF (5 mL) was added [1-(4-chloroethoxy)naphthyl](3-chloro-4-hydroxy)benzoic acid hydrazide (0.41g, 1 mmole) and triethylamine (0.1 g, 1mmole). The resulting solution was heated at 80°C overnight. Removal of most of the solvent in vacuo followed by flash chromatography (10:1 $CHCl_3$/MeOH) on silica gel provided the title compound as a brown solid.

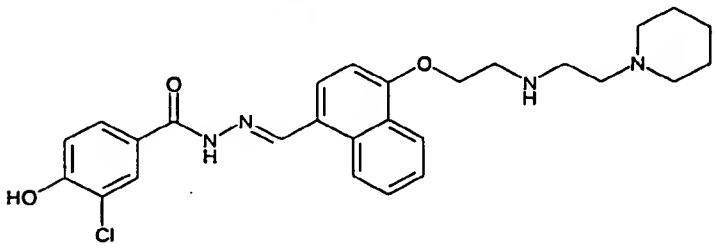
3-Chloro-4-hydroxybenzoic acid {3,5-dimethoxy-4-[2-(4-trifluoromethoxybenzylamino)-ethoxy]benzylidene}hydrazide



^{1}H NMR (CD_3OD): δ 2.90 (brd t, 2H), 3.75 (s, 6H), 3.89 (s, 2H), 4.08 (brd t, 2H), 6.87 (d, 1H), 7.10 (s, 2H), 7.20 (d, 2H), 7.43 (d, 2H), 7.65 (m, 1H), 7.82 (m, 1H), 8.11 (brd s, 1H); MS (APCI): 567.9.

EXAMPLE 146:

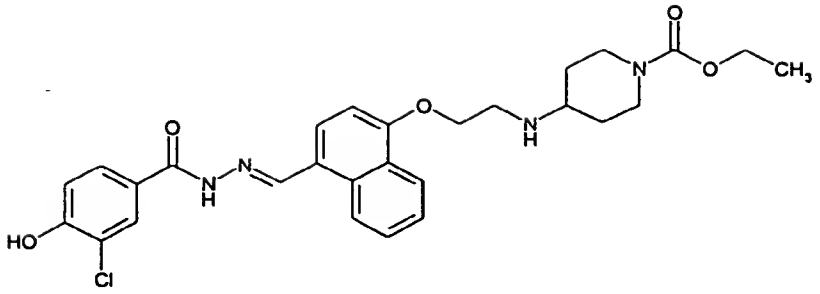
3-Chloro-4-hydroxybenzoic acid {4-[2-(2-piperidin-1-yl-ethylamino)ethoxy]naphth-1-ylmethylene}hydrazide



^{1}H NMR (DMSO-d_6): δ 1.53 (m, 2H), 1.74 (m, 4H), 3.12 (m, 2H), 3.40 (m, 2H), 3.54 (m, 2H), 3.63 (m, 4H), 4.52 (s, 2H), 7.10 (d,1H), 7.14 (d, 1H), 7.60 (t, 1H), 7.71 (m,1H), 7.80 (dd, 1H), 7.83 (d, 1H), 8.00 (d,1H), 8.51 (d, 1H), 8.95 (d, 1H), 8.98 (s, 1H), 11.69 (s,1H); MS (APCI): 495.0

EXAMPLE 147:

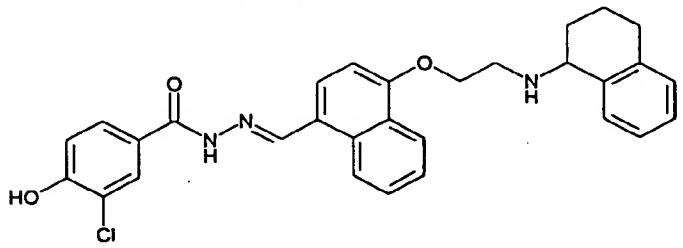
3-Chloro-4-hydroxybenzoic acid {4-[2-(3-diethylaminopropylamino)ethoxy]naphth-1-ylmethylene}hydrazide



^{1}H NMR (DMSO-d_6): δ 1,10 (t, 3H), 1.15 - 1.23 (m, 2H), 1.86 (m, 2H), 2.79 (m, 3H), 3.30 (m, 2H), 3.87 (m, 2H), 3.94 (q, 2H), 4.28 (m, 2H), 7.03 (d,1H), 7.05 (m, 1H), 7.51 - 7.63 (m, 3H), 7.13 (d, 1H), 7.75 (m,1 H), 7.93 (d, 1H), 8.29 (d,1 H), 8.87 (m,2 H), 11.55 (s, 1H); MS (APCI): 539.1, 541.0.

EXAMPLE 150:

3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydronaphth-1-ylamino)ethoxy]-naphth-1-ylmethylene}hydrazide

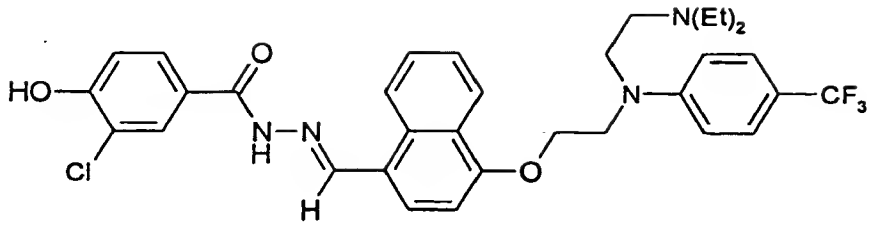


^{1}H NMR (DMSO-d_6): δ 1.76 (m, 1H), 2.04 (m, 1H), 2.17 (m, 2H), 2.75 - 2.94 (m, 2H), 3.61 (m, 2H), 4.55 (m,2H), 4.71(s, 1H), 7.11 (d, 1H), 7.13 (d, 1H), 7.23 - 7.35 (m, 3H), 7.61 (d, 1H), 7.67 (d,1H), 7.71 (dd, 1H), 7.81 (dd, 1H), 7.86 (d, 1H), 8.01(d, 1H), 8.48 (d, 1H), 8.94 (m, 1H), 8.99 (m, 1H), 9.22 (m, 2H), 11.00 (s,1 H), 11.64 (s,1H); MS (APCI): 514.0, 516.0

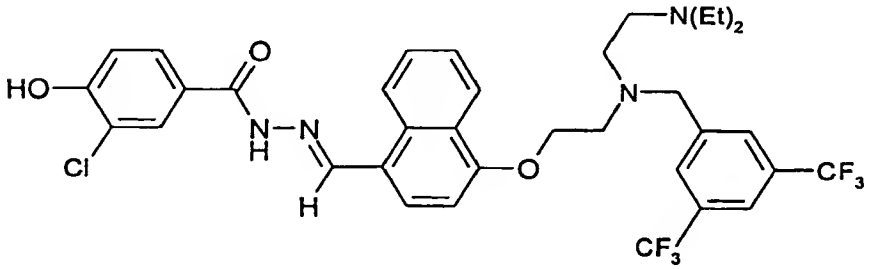
EXAMPLE 151:

1-(2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}ethyl)piperidine-4-carboxylic acid amide

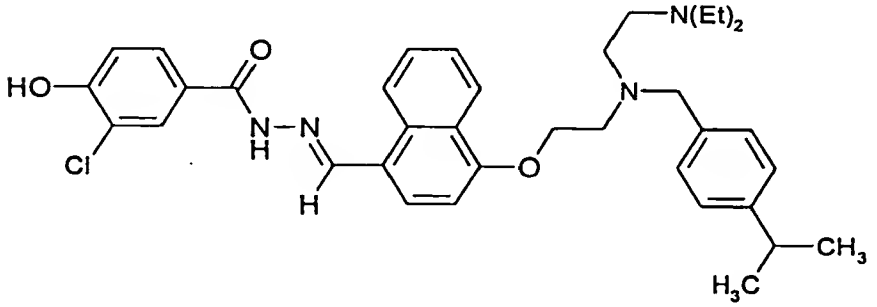
EXAMPLE 155:



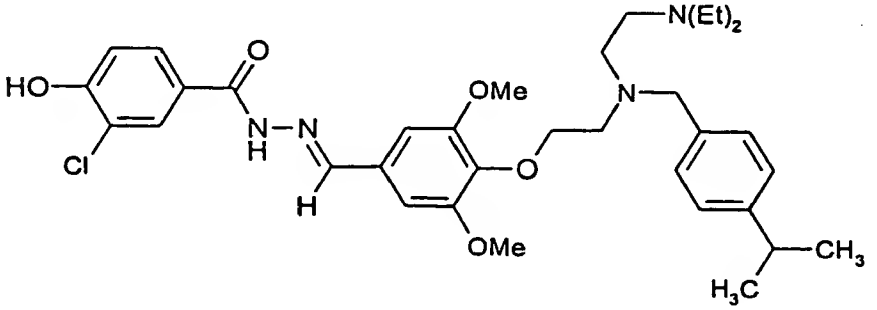
EXAMPLE 156:

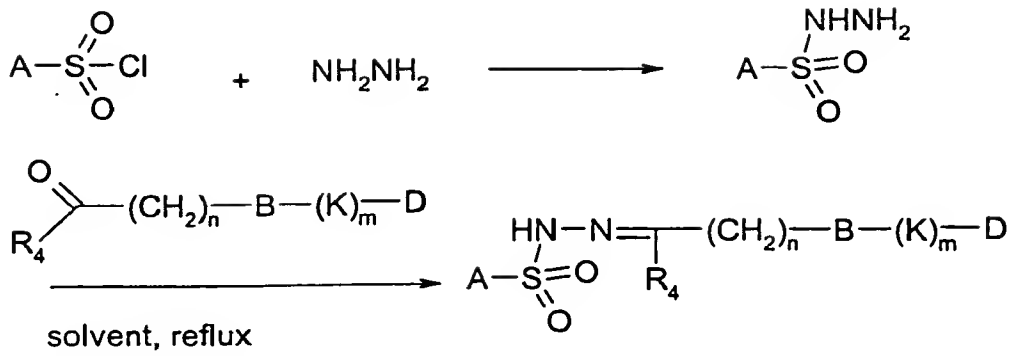


EXAMPLE 157:



EXAMPLE 158:





wherein A, B, K, D, m, n and R^4 are as defined for formula I.

The synthesis of the arylsulfonylhydrazide precursors is performed by application of general methodology, for example as described by Friedman, L.; Litle, R.L; Reichle, W. R. in *Org. Synth. Coll. Vol. V*, 1973, 1055-1057, by slowly adding the arylsulfonyl chloride either neat, or in a solution in an inert solvent such as tetrahydrofuran, dimethyl ether, dioxane or diethyl ether to an excess of hydrazine, either neat or in solution in the one of the above solvents or a mixture of these at -20°C to 100°C, preferably between 0°C to 60°C. When the reaction is judged to be completed, the excess of solvent and volatile reagents is removed by distillation either at atmospheric pressure or in vacuo. The residual product can be further purified by recrystallization from a solvent such as methyl alcohol, ethyl alcohol, isopropyl alcohol, water, toluene, acetic acid, dioxane, tetrahydrofuran or a mixture of two or more of the above solvents when compatible.

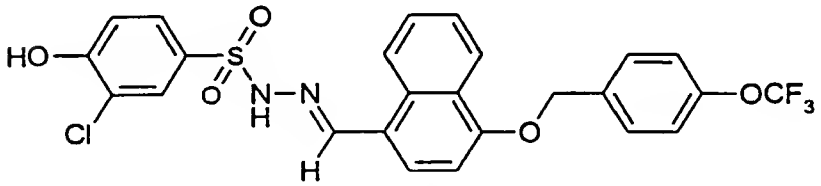
Alternatively, the product can be purified by column chromatography using dichloromethane/-methanol or chloroform/methanol or isopropyl alcohol as eluent. The corresponding fractions are concentrated either at atmospheric pressure or in vacuo to provide the pure arylsulfonyl hydrazide.

By use of the above methodology the following compounds can be prepared:

EXAMPLE 161:

3-Chloro-4-hydroxybenzenesulfonic acid (benzylidene)hydrazide

3-Chloro-4-hydroxy-benzenesulfonic acid [4-(4-trifluoromethoxybenzyloxy)-1-naphthylmethylene]hydrazide

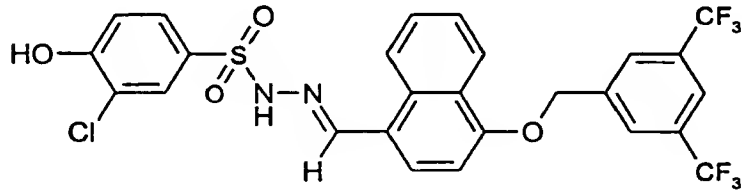


To a solution of 3-chloro-4-hydroxy-benzene sulfonyl hydrazide (105 mg, 0.48 mmol) in 5 ml methanol was added 4-trifluoromethoxybenzyloxy-1-naphthaldehyde (163 mg, 0.49 mmol) and a catalytical amount of glacial acetic acid (5 drops). The reaction mixture was stirred overnight, and filtered. The filtrate was concentrated under vacuo to give the crude product. Flash chromatography (silica gel, 1:1 hexane/ethylacetate) provided 145 mg (56%) of the title compound as a solid.

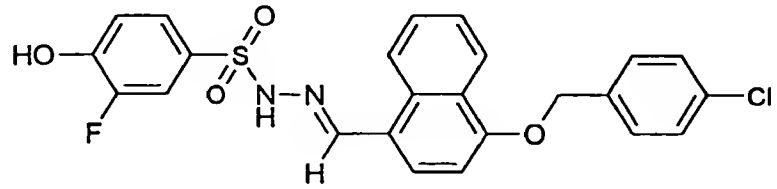
^{1}H NMR (DMSO-d_6) δ 5.27 (s, 2 H), 6.06 (s, 1 H), 6.83 (d, J = 8.1 Hz, 1 H), 7.10 (d, J = 8.1 Hz, 1 H), 7.26 (d, J = 7.3 Hz, 2 H), 7.50 - 7.60 (m, 5 H), 7.80 (s, 1 H), 7.85 (dd, J = 3.0, 8.2 Hz, 1 H), 8.08 (d, J = 2.1 Hz, 1 H), 8.26 (s, 1 H), 8.36 (d, J = 7.76 Hz, 1 H), 8.67 (d, J = 8.5 Hz, 1 H). CIMS m/z: 551, 553.

By using the above methodology, the following compounds may be prepared:

EXAMPLE 163:



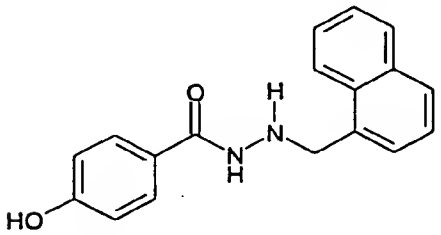
EXAMPLE 164:



a compatible mixture of two or more solvents. Optionally a small amount of an acid is used as a catalyst such as hydrochloric acid, trifluoroacetic acid, acetic acid, or sulfuric acid. The reactions are performed at 0°C to 60°C, preferably at 10°C to 30°C. When the reaction is complete as judged by HPLC or TLC (silica gel, 1% methanol in dichloromethane as eluent) the solvent(s) are removed and the residue is chromatographed on a silica gel column using 1% methanol in dichloromethane or chloroform as an eluent. The corresponding fractions are concentrated to give the desired product. Specific examples illustrating the preparation of alkylhydrazides according to the invention are provided below.

EXAMPLE 167:

4-hydroxybenzoic acid (1-naphthylmethyl)hydrazide



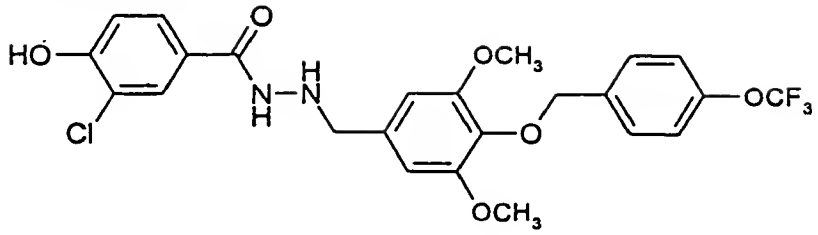
4-Hydroxybenzoic acid (1-naphthylmethylene)hydrazide (100 mg, 0.34 mmol) was dissolved in methanol (10 mL) and treated with sodium cyanoborohydride (236 mg, 4.1 mmol) followed by two drops of trifluoroacetic acid. After stirring the reaction solution for three hours at room temperature, the solvent was evaporated in vacuo. The residue was introduced into a silica gel column and eluted with dichloromethane/methanol (99/1). Evaporation of the corresponding fractions in vacuo gave the title compound in 30% yield. MS (ESI) m/z 293 $(M+H)^+$.

Using the same methodology as described above the following compound was prepared:

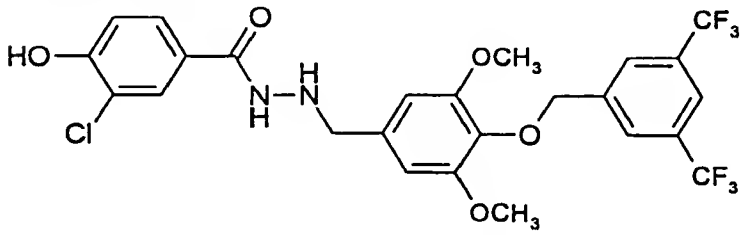
EXAMPLE 168:

3-Chloro-4-hydroxybenzoic acid N-[4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzyl]hydra-zide

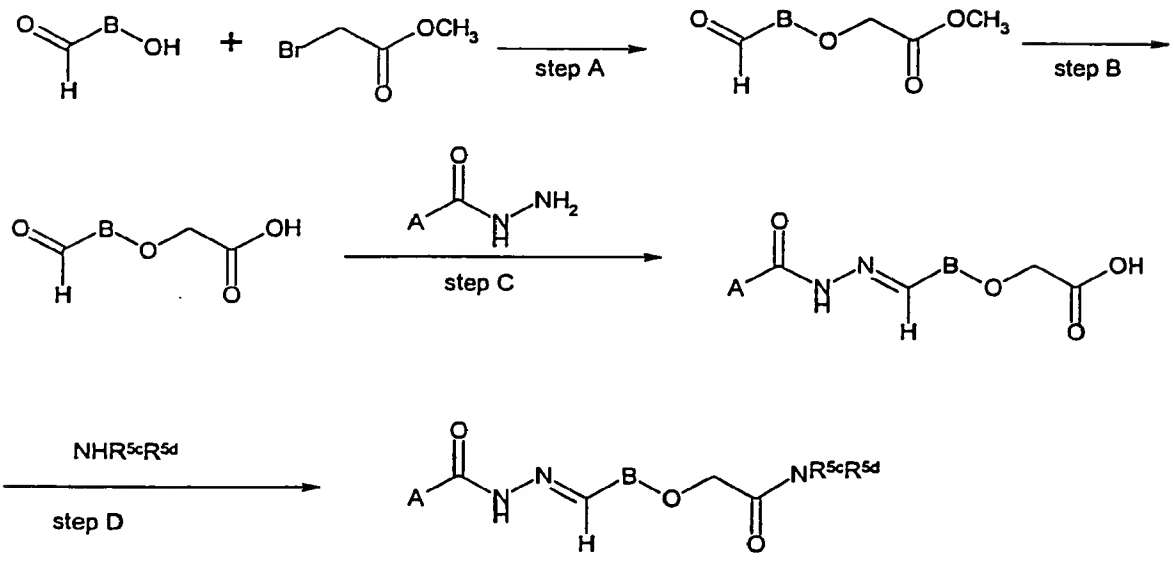
EXAMPLE 172:



EXAMPLE 173:

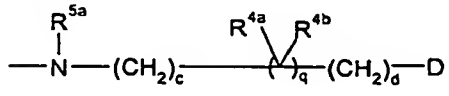


General procedure for synthesis of compounds of the general formula XI:



formula XI

A and B are as defined for formula I and -$NR^{5c}R^{5d}$ is



where R^{5a}, R^{4a}, R^{4b}, c, q, d and D are as defined for formula I or

-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step C: The resulting carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

Step D: The resulting acid is then coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or an acid halide that can then react with the amine to give a compound of formula XI. Step D can also be done combinatorially with a selected number of amines. The product can then be isolated either by filtration or by extraction using a solvent such as ethyl acetate, toluene, dichloromethane or diethylether and the solvent may then be removed by concentration at atmospheric or reduced pressure. The product can be further purified by either recrystallization from a solvent such as ethyl alcohol, methyl alcohol, isopropyl alcohol, toluene, xylene, hexane, tetrahydrofuran, diethyl ether, dibutyl ether, water or a mixture of two or more of the above. Alternatively, the product can be purified by column chromatography using dichloromethane/methanol or chloroform/methanol or isopropyl alcohol as eluent giving a compound of formula XI.

Specific examples illustrating the preparation of compounds of the general formula XI according to the invention are provided below.

^{1}H NMR (DMSO-d_6): δ 4.91 (s, 2H), 6.95 (d, 1H), 7.02 (d, 1H), 7.55 (t, 1H), 7.64 (t, 1H), 7.74 (d, 1H), 7.92 (d, 1H), 8.27 (d, 1H), 8.90 (m, 2H), 10.92 (brd s, 1H), 11.63 (s, 1H), 13.14 (brd s, 1H).

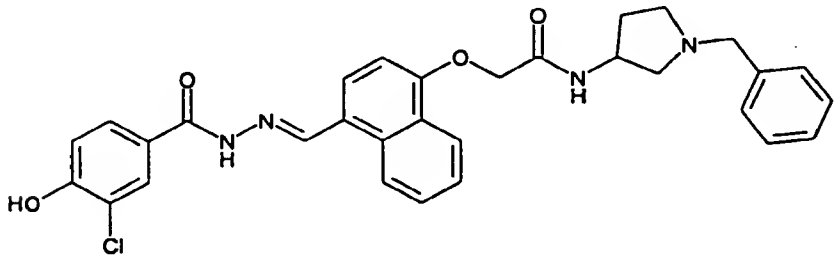
Step D: To a solution of the hydrazone-carboxylic acid (50 mmol) in anhydrous DMSO was added a solution of carbonyldiimidazole (55 mmol) in anhydrous DMSO. After the evolution of gases ceased (approximately 3-4 minutes), the amine was added and the reaction mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate and washed with water, brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the crude material, which was purified by reverse phase HPLC chromatography to give the title compound.

^{1}H NMR (DMSO-d_6): δ 4.99 (s, 2H), 7.04 (m, 2H), 7.36 (d, 2H), 7.65 (m, 4H), 7.79 (t, 2H), 7.99 (s, 1H), 8.40 (d, 1H), 8.72 (s, 1H), 8.92 (d, 1H), 10.42 (s, 1H), 10.96 (s, 1H), 11.69 (s, 1H); MS (APCI): 507.9.

By using the same methodology, the following compounds were prepared:

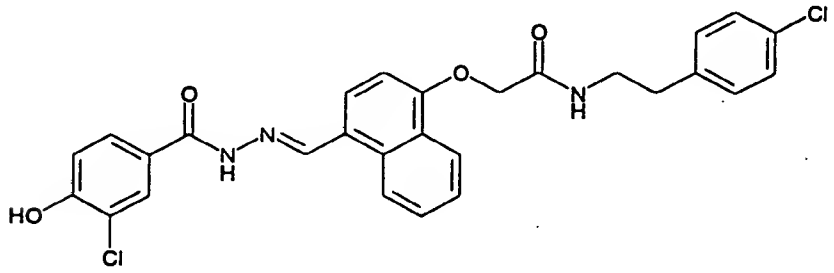
EXAMPLE 175:

N-(1-Benzylpyrrolidin-3-yl)-2-{4-[(3-chloro-4-hydroxy-benzoyl)hydrazonomethyl]naphth-1-yloxy}acetamide



EXAMPLE 178:

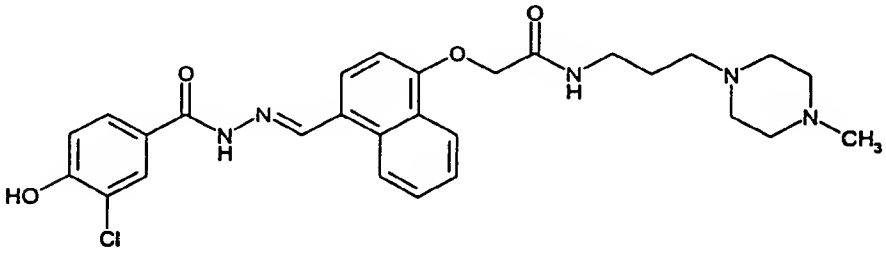
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-[2-(4-chlorophenyl)ethyl]acetamide



^{1}H NMR (DMSO-d_6): δ 2.40 (t, 2H), 2.79 (t, 2H), 4.74 (s, 2H), 6.96 (d, 1H), 7.10 (d, 1H), 7.63 (t, 1H), 7.69 (t, 1H), 7.72 (m, 2H), 7.81 (s, 1H), 8.01 (m, 2H), 8.23 (t, 1H), 8.40 (d, 1H), 8.95 (s, 1H), 9.01 (d, 1H), 10.98 (brd s, 1H), 11.70 (s, 1H); MS (APCI) 538.8, 537.8.

EXAMPLE 179:

2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-[3-(4-methylpiperazin-1-yl)propyl]acetamide



^{1}H NMR (DMSO-d_6): δ 1.50 (m, 2H), 2.26 (m, 2H), 2.48 (m, 5H), 3.01 (m, 8H), 4.53 (s, 2H), 6.78 (d, 1H), 6.89 (d, 1H), 7.38 (t, 1H), 7.47 (t, 1H), 7.5 (t, 2H), 7.76 (d, 1H), 8.01 (t, 1H), 8.22 (d, 1H), 8.68 (d, 1H), 8.74 (s, 1H), 10.74 (brd s, 1H), 11.45 (s, 1H); MS (APCI): 538.0.

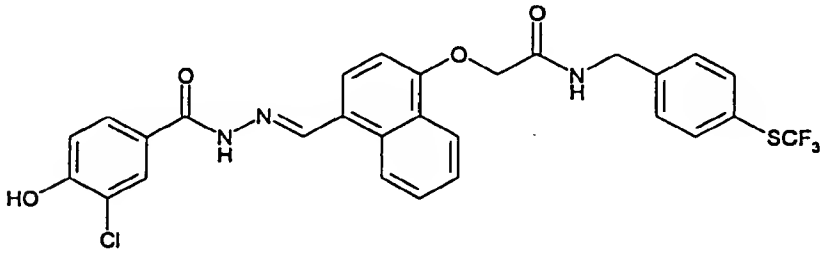
EXAMPLE 180:

3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2-oxoethoxy]-naphth-1-ylmethylene}hydrazide

MS (APCI): 636, 638.

EXAMPLE 183:

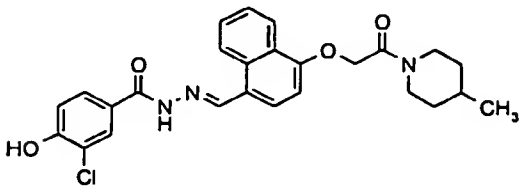
2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-yloxy}-N-(4-trifluoromethylsulfanylbenzyl)acetamide



^{1}H NMR (DMSO-d_6): δ 4.48 (d, 2H), 4.88 (s, 2H), 7.08 (m, 2H), 7.45 (d, 2H), 7.68 (m, 4H), 7.82 (m, 2H), 8.01 (d, 1H), 8.52 (d, 1H), 8.87 (t, 1H), 8.96 (s, 1H), 9.01 (d, 1H), 10.98 (brd s, 1H), 11.72 (s, 1H); MS (APCI): 588.2

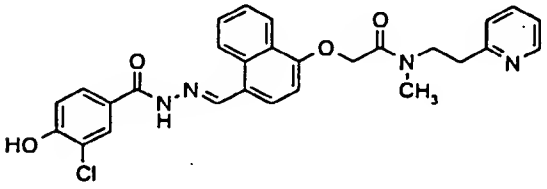
7.68 (t, 1H), 7.78 (dd, 2H), 8.00 (d, 1H), 8.34 (m, 1H), 8.94 (s, 1H), 9.00 (d, 1H), 11.65 (brd s, 1H); MS (APCI): 495.2, 497.2.

EXAMPLE 187:



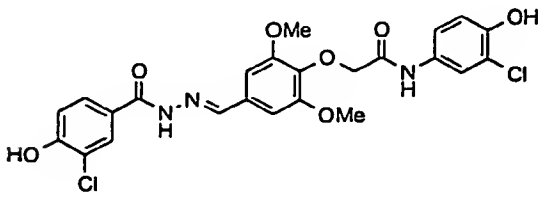
^{1}H NMR (DMSO-D_6): δ 0.86 (s, 3H), 1.48 (m, 4H), 2.38 (t, 1H), 2.72 (m, 1H), 3.09 (t, 1H), 3.84 (t, 1H), 4.18 (t, 1H), 5.09 (m, 2H), 7.03 (d, 1H), 7.11 (d, 1H), 7.59 (t, 1H), 7.64 (t, 1H), 7.82 (d, 2H), 8.01 (s, 1H), 8.33 (d, 1H), 8.94 (s, 1H), 9.00 (d, 1H), 11.0 (brd, 1H), 11.69 (brd s, 1H); MS (APCI): 480.1, 482.1.

EXAMPLE 188:

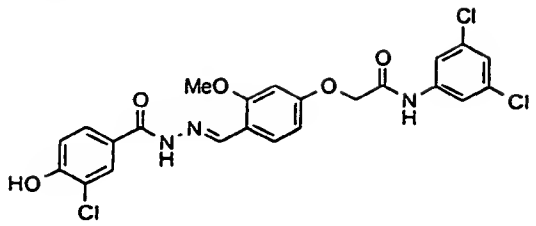


^{1}H NMR (DMSO-D_6): δ 2.88 (s, 1.5H) + (s, 1.5H), 3H], 2.95 (t, 1H), 3.01 (s, 1.5H), 3.10 (s, 1.5H), 3.10 (t, 1H), 3.69 (t, 1H), 3.81 (t, 1H), 5.05 (d, 2H), [6.66 + 6.95 (d), 1H], 7.10 (d, 1H), [7.20 + 7.38 (d), 1H], 7.29 (d, 1H), 7.67 (m, 5H), 8.01 (s, 1H), 8.30 (t, 1H), 8.53 (dd, 1H), 8.97 (m, 2H), 11.67 (brd s, 1H); MS (APCI): 517.3, 519.2.

EXAMPLE 189:

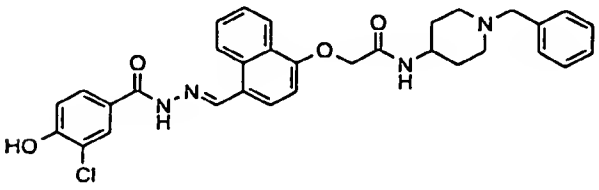


EXAMPLE 192:



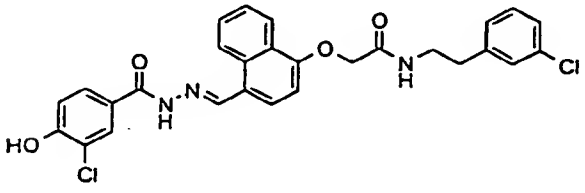
^{1}H NMR (DMSO-D_6): δ 4.06 (s, 3H), 4.94 (s, 2H), 6.81 (d, 1H), 6.89 (s, 1H), 7.19 (d, 1H), 7.45 (s, 1H), 7.90 (m, 3H), 8.10 (s, 1H), 8.82 (s, 1H), 10.62 (s, 1H), 11.07 (brd s, 1H), 11.75 (s, 1H); MS (APCI): 523.3, 524.8, 526.6.

EXAMPLE 193:

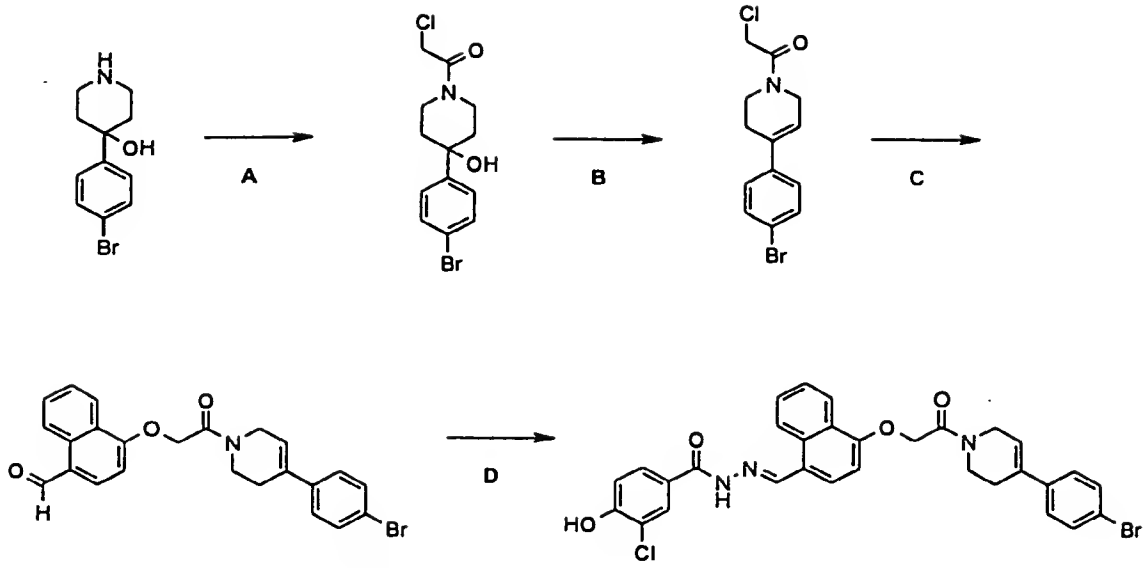


^{1}H NMR (DMSO-D_6): δ 1.68 (m, 2H), 2.01 (m, 2H), 3.05 (m, 2H), 3.35 (m, 2H), 3.86 (m, 1H), 4.26 (s, 2h), 4.81 (s, 2H), 6.95 (d, 1H), 7.09 (d, 1H), 7.46 (s, 5H), 7.59 (m, 1H), 7.66 (t, 1H), 7.77 (d, 1H), 7.98 (d, 1H), 8.34 (d, 1H), 8.41 (d, 1H), 8.92 (m, 2H), 9.65 (brd s, 1H), 11.02 (brd s, 1H), 11.80 (brd s, 1H); MS (APCI): 571.3, 572.3, 573.3.

EXAMPLE 194:



^{1}H NMR (DMSO-D_6): δ 2.79 (t, 2H), 3.43 (qt, 2H), 4.71 (s, 2H), 6.95 (d, 1H), 7.08 (d, 1H), 7.17 (m, 1H), 7.26 - 7.30 (m, 3H), 7.61 (t, 1H), 7.67 (t, 1H), 7.76 (m, 2H), 7.99 (d, 1H), 8.24



4-(4-bromophenyl)-4-piperidinol chloroacetamide (step A):

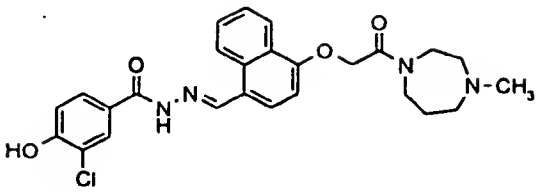
To a solution of 4-(4-bromophenyl)-4-piperidinol (5 g, 19.5 mmol) and diisopropylethylamine (2.8 g, 21.5 mmol) in DMF (30 mL) was added dropwise chloroacetylchloride (2.2 g, 21.5 mmol). After stirring the mixture for one hour, the mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (2x), 1 N HCl (3x), water, brine, and dried over $MgSO_4$. The solution was concentrated and chromatographed over silica gel with ethyl acetate to give the product as a brown solid (4 g, 62 %).

^1H NMR (DMSO-D_6): δ 1.21 (d, 2H), 1.71 (t. 1H), 1.96 (t, 1H), 2.71 (t, 1H), 3.37 (t, 1H), 3.70 (d, 1H), 4.27 (d, 1H), 4.54 (s, 2H), 5.26 (s, 1H), 7.42 (d, 2H), 7.51 (d, 2H).

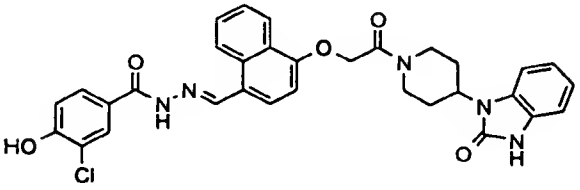
4-(4-bromophenyl)-3,4-dihydropiperidine chloroacetamide (step B):

To a solution of 4-(4-bromophenyl)-4-piperidinol chloroacetamide (4 g, 12 mmol) and diisopropylethylamine (4.6 mL, 26 mmol) in THF (40 mL) cooled in an ice-bath was added methanesulfonyl chloride (2 mL, 26 mmol) and the mixture was refluxed for 16 hours under a nitrogen blanket. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl (2x), aqueous $NaHCO_3$ (2x), brine (2x), and dried over $MgSO_4$. The solvent was evaporated and the product was chromotographed over silica gel with ethyl acetate/hexane (4/6). The product was obtained as a yellow solid (1.5 g, 32%).

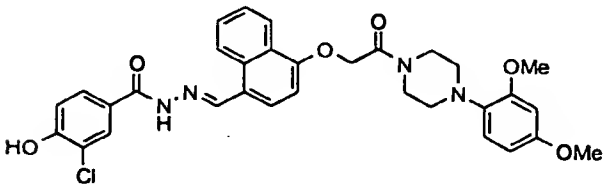
EXAMPLE 197:



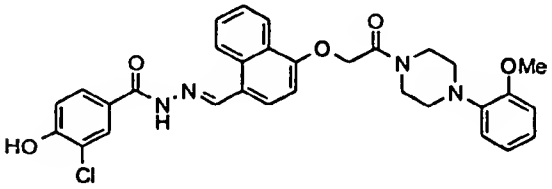
EXAMPLE 198:



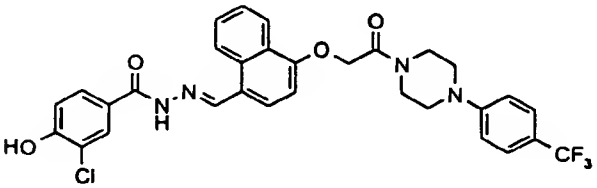
EXAMPLE 199:



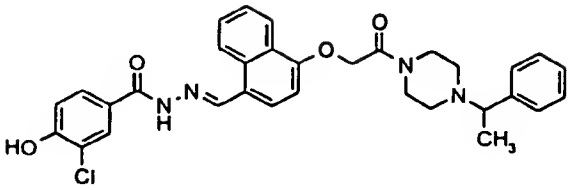
EXAMPLE 200:



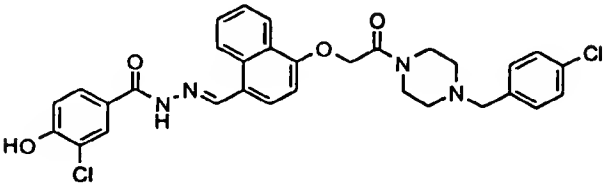
EXAMPLE 201:



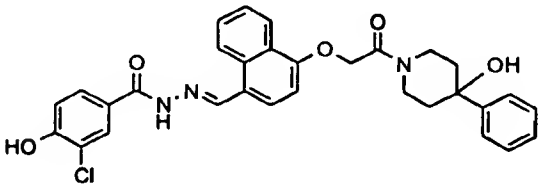
EXAMPLE 202:



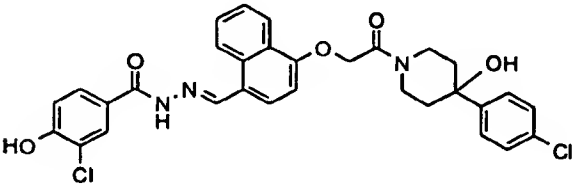
EXAMPLE 203:



EXAMPLE 204:



EXAMPLE 205:



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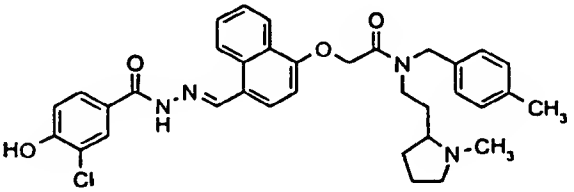
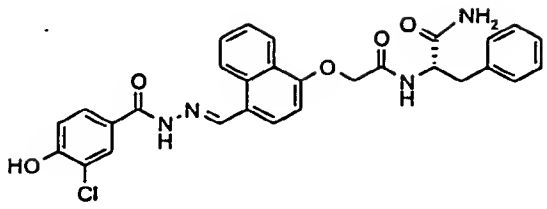
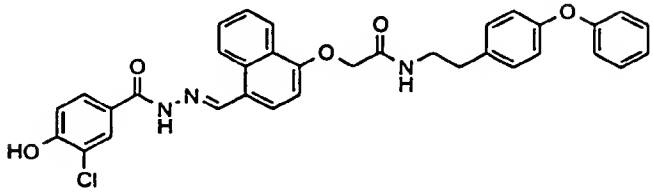


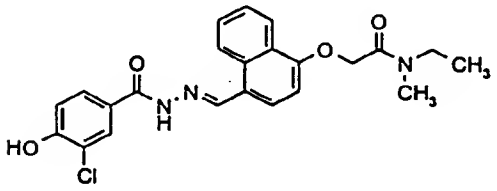
EXAMPLE 217:



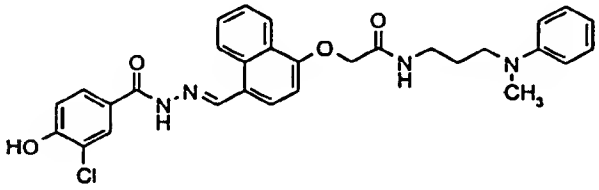
EXAMPLE 218:



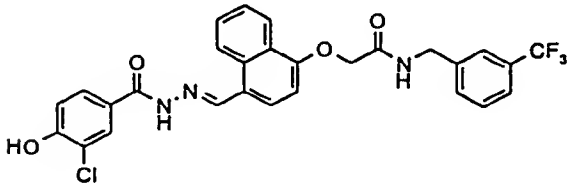
EXAMPLE 219:



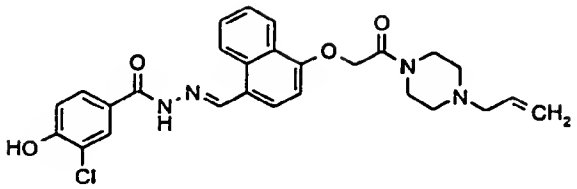
EXAMPLE 220:



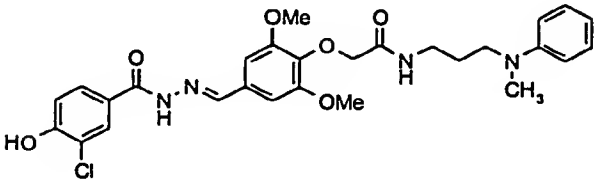
EXAMPLE 221:



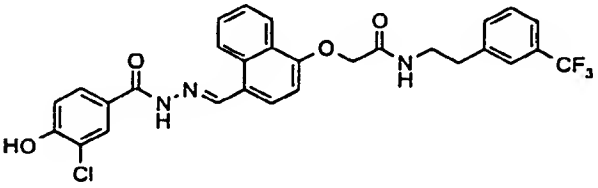
EXAMPLE 222:



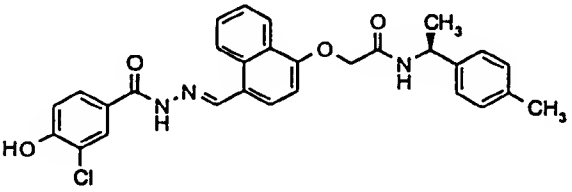
EXAMPLE 223:



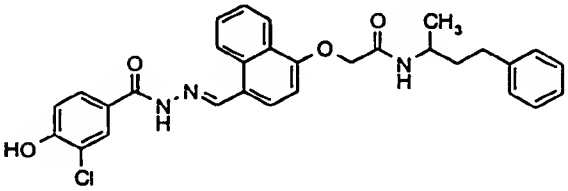
EXAMPLE 224:



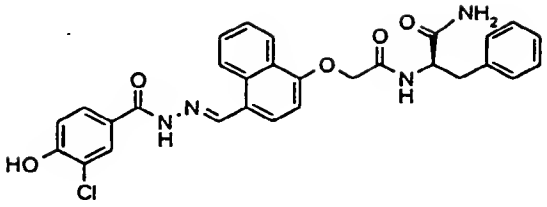
EXAMPLE 225:



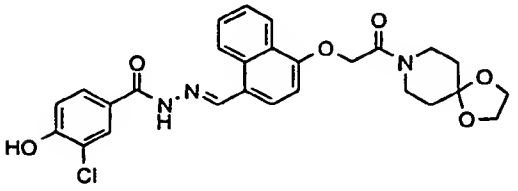
EXAMPLE 226:



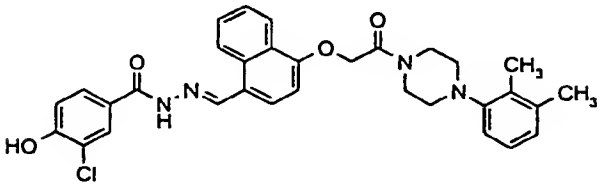
EXAMPLE 237:



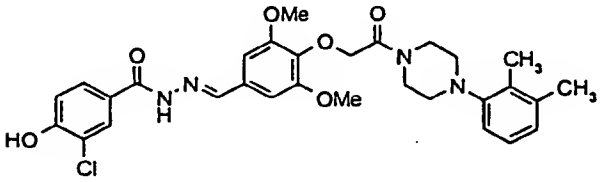
EXAMPLE 238:



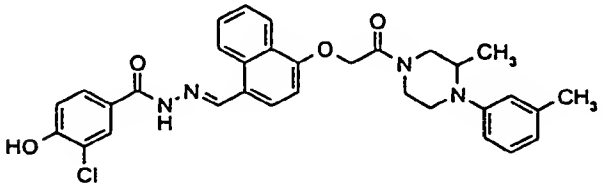
EXAMPLE 239:



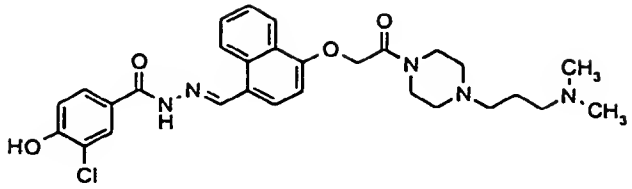
EXAMPLE 240:



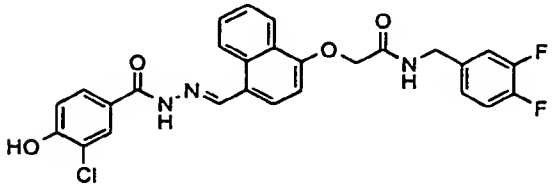
EXAMPLE 241:



EXAMPLE 242:



EXAMPLE 243:



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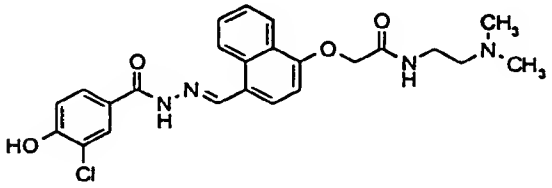

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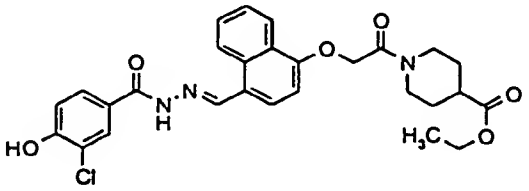
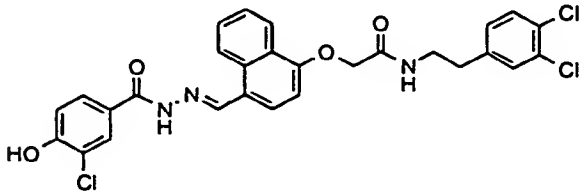


EXAMPLE 246:



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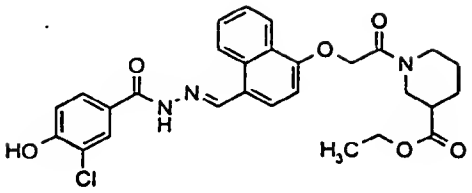
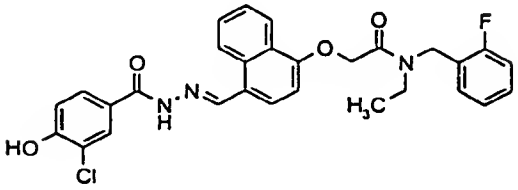
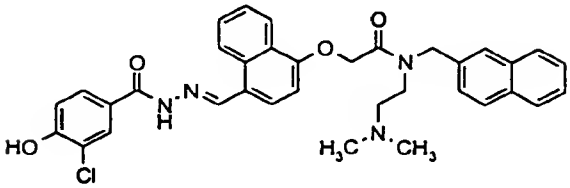


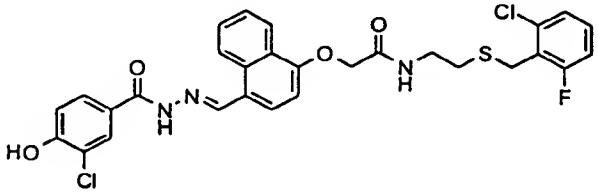
EXAMPLE 258:



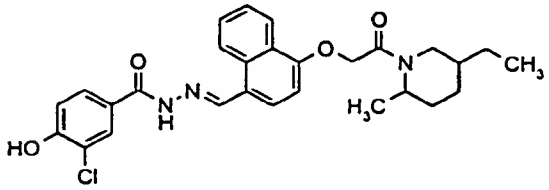
EXAMPLE 259:



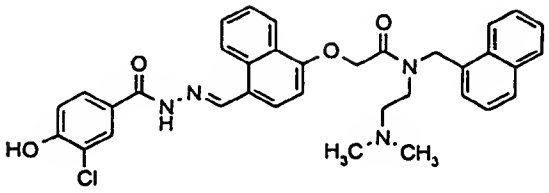
EXAMPLE 260:



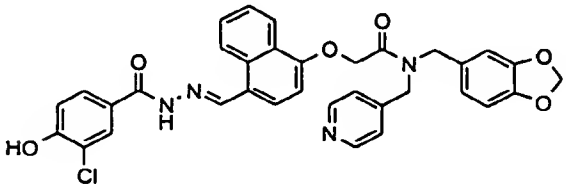
EXAMPLE 261:



EXAMPLE 262:



EXAMPLE 263:



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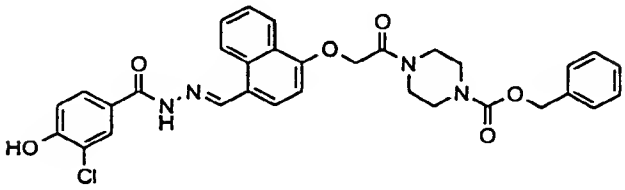

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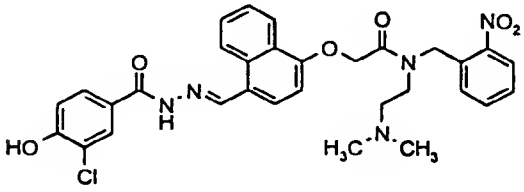
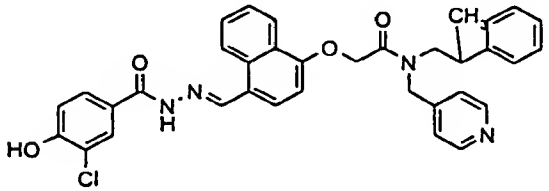
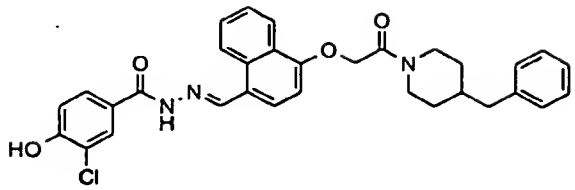


EXAMPLE: 266



EXAMPLE 277:



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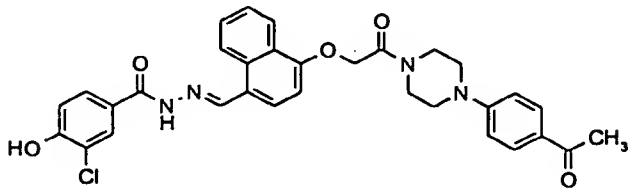

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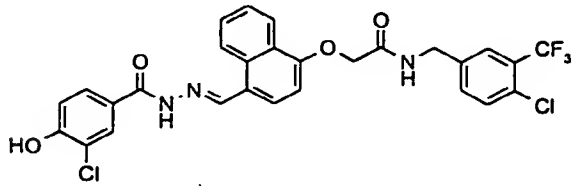

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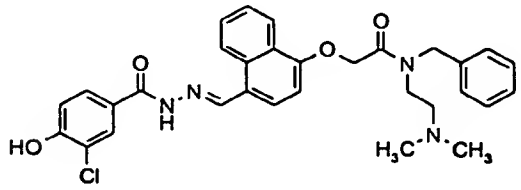

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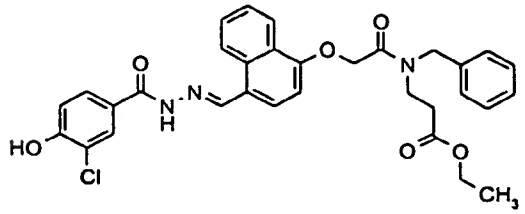

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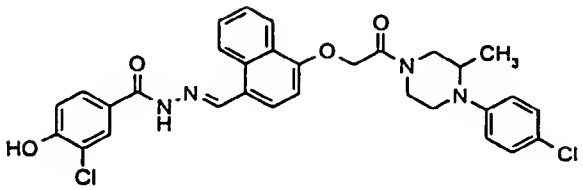

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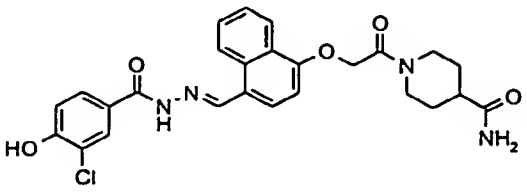

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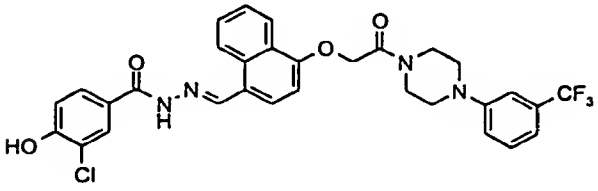

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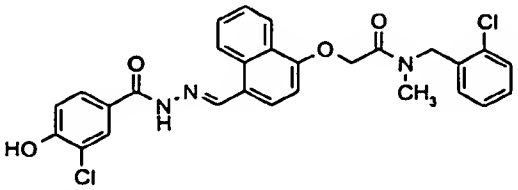

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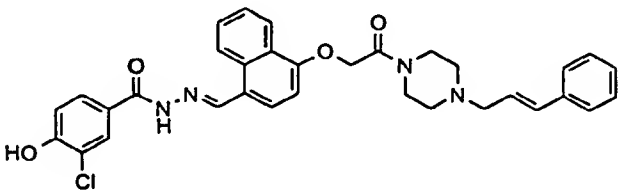

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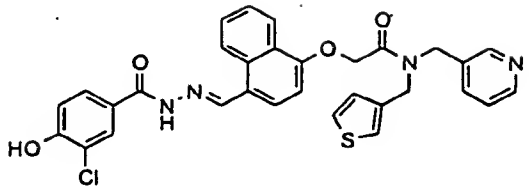

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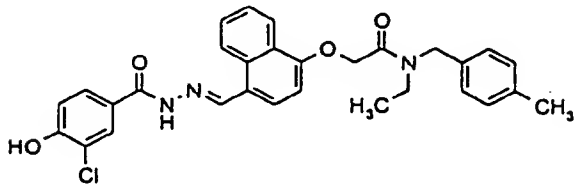

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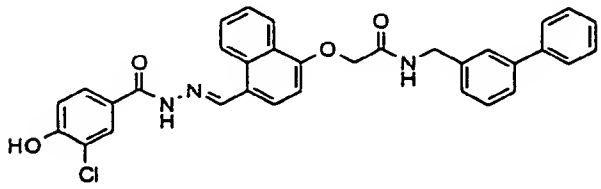

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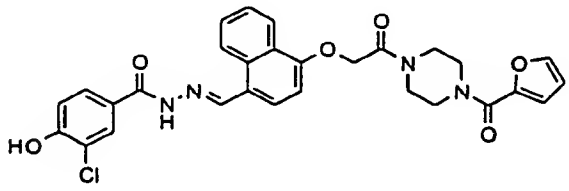

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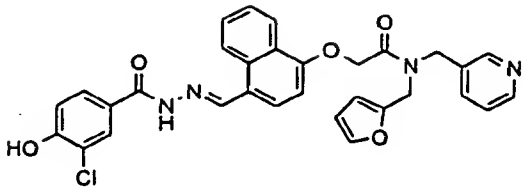

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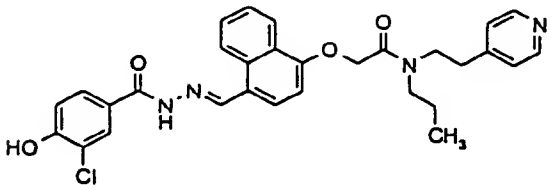

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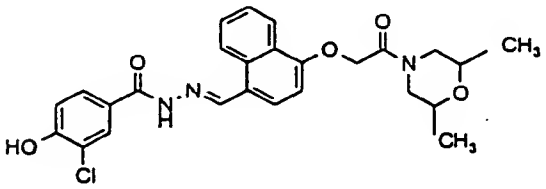

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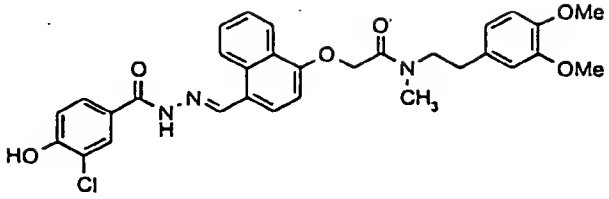

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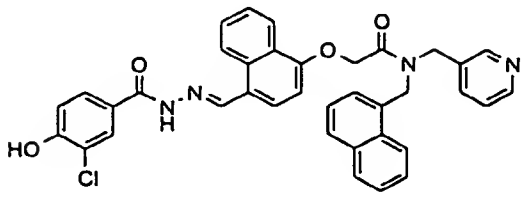

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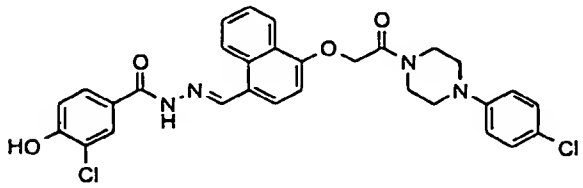

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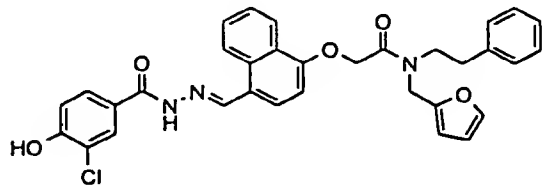

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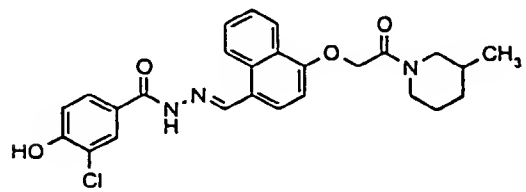

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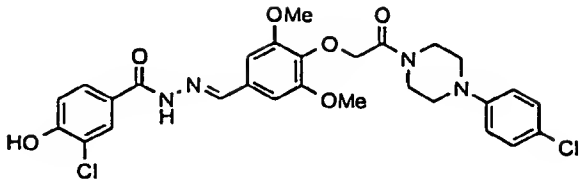

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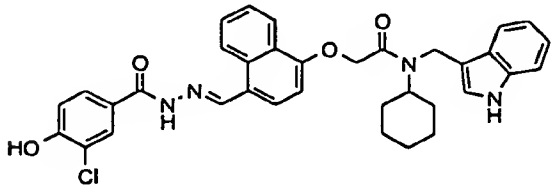

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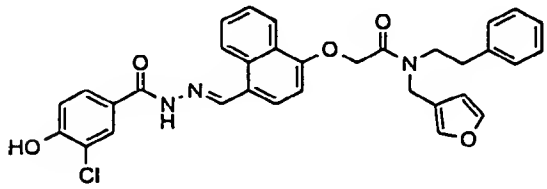

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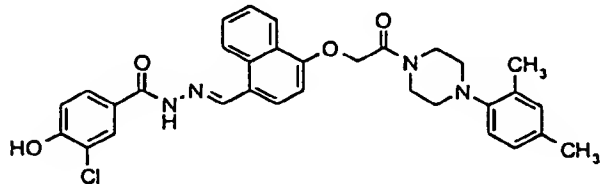

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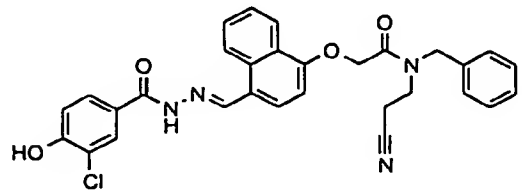

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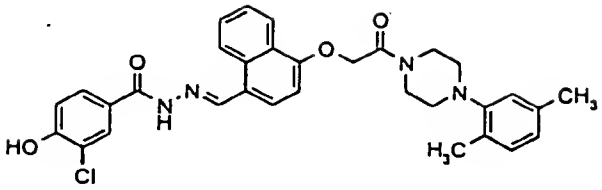

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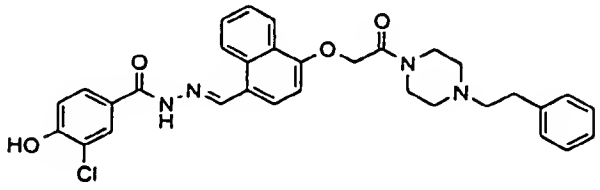

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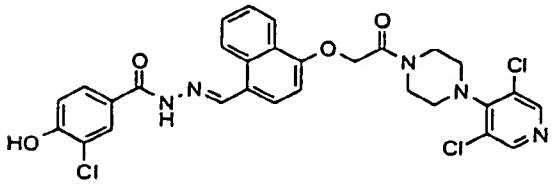

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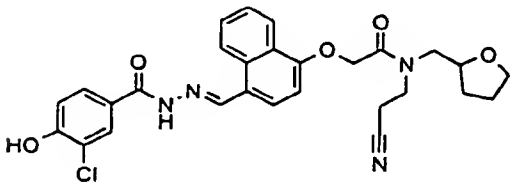

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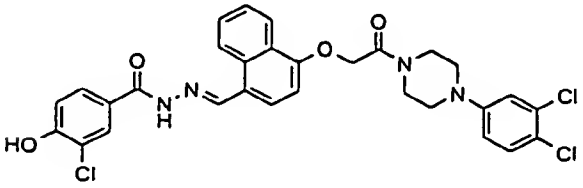

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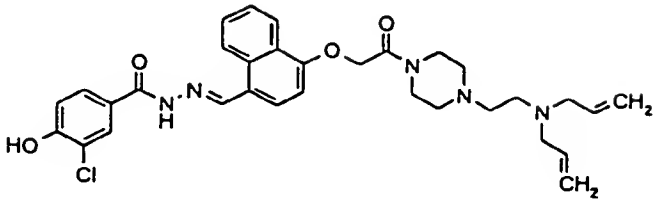

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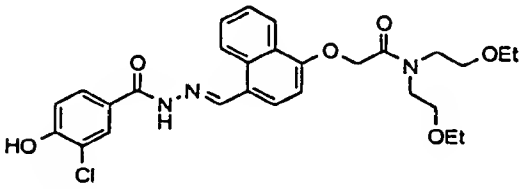

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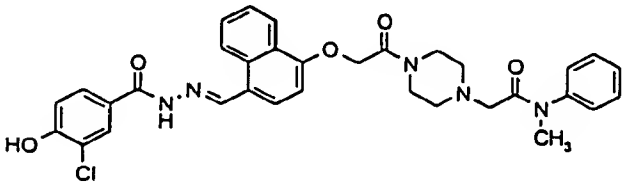

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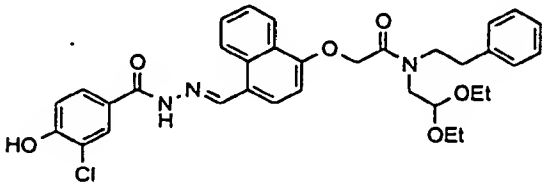
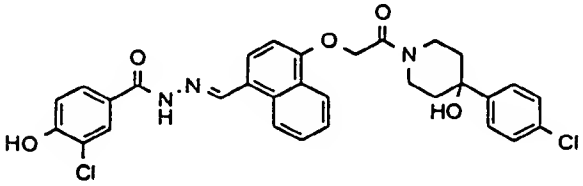
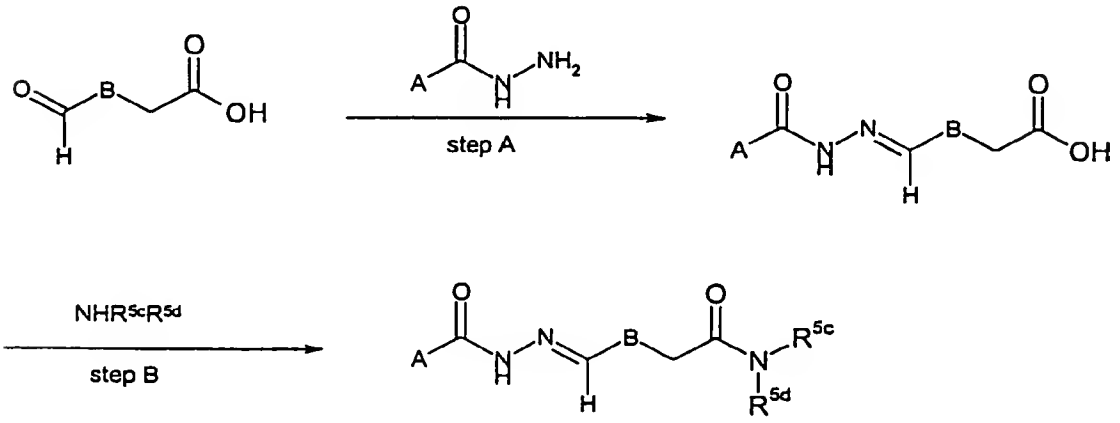


EXAMPLE 341:

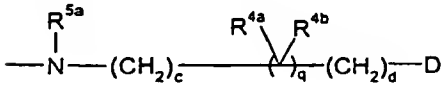


General procedure for synthesis of compounds of the general formula XII:



formula XII

A and B are as defined for formula I and -$NR^{5c}R^{5d}$ is

 where R^{5a}, R^{4a}, R^{4b}, c, q, d and D are as defined for formula I or

-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

^{1}H NMR (DMSO-D_6): δ 4.1 (s, 2H), 7.1 (d, 1H), 7.5 (d, 1H), 7.7 (qt, 2H), 7.8 (d, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 8.1 (d, 1H), 8.8 (d, 1H), 9.1 (s, 1H), 11.0 (brd s, 1H), 11.8 (s, 1H), 12.2 (brd s, 1H); MS (APCI): 383.4, 385.2.

Preparation of (3-formylindolyl)acetic acid:

Ethyl (3-formylindolyl)acetate:
3-Formylindole (10.0 g, 69 mmoles) was dissolved in DMF (100 ml). Under N_2 was a 60% suspension of NaH in mineral oil (3.0 g) added in portions with cooling (temp < 15 °C). At < 15 °C was a solution of ethyl bromoacetate (8.4 ml) in DMF (15 ml) added drop wise over 30 minutes. The resulting mixture was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was added water (300 ml) and extracted with ethyl acetate (2 x 150 ml), the combined organic extracts were washed with satd. NH_4Cl, dried ($MgSO_4$) and concentrated to afford 15.9 g ethyl (3-formylindolyl)acetate.

^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H), 4.22 (q, 2H), 4.90 (s, 2H), 7.21 - 7.35 (m, 3H), 7.72 (s, 1H), 8.30 (d, 1H), 10.0 (s, 1H).

(3-formylindolyl)acetic acid:
Ethyl (3-formylindolyl)acetate (15.9 g) was dissolved in 1,4-dioxane (100 ml) and added 36% aq. NaOH (10 ml). The resulting mixture was stirred at room temperature for 4 days. Water (500 ml) was added and the mixture was washed with diethyl ether (150 ml). The aqueous phase was made acidic with 5N HCl and extracted with ethyl acetate (250 + 150 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 10.3 g (73 % over two steps) of (3-formylindolyl)acetic acid.

^{1}H NMR (DMSO-d_6) δ 4.94 (s, 2H), 7.27 - 7.36 (m, 3H), 7.98 (s, 1H), 8.25 (d, 1H), 10.0 (s, 1H), 12.5 (bs, 1H).

Preparation of (4-Formylindolyl)acetic acid:

4-Formylindole:

^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 6.65 (d, J = 3.6 Hz, 1H), 7.19 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 3.6 Hz, 1H), 7.63 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H).

5-Formyl-N-tosylindole:

To a solution of 5-cyano-N-tosylindole (0.66 g, 2.2 mmol) in anhydrous THF (20 mL), was added 1M DIBAL in hexane (4 mL, 4 mmol) via syringe at 0°C. The mixture was stirred at room temperature for 16 h, poured into ice-cooled 1N hydrochloric acid (50 mL), extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated to give an oil. After a short column chromatography using hexane/ethyl acetate 2: 1 as eluent 0.62 g (95%) pure 5-formyl-N-tosylindole was obtained.

^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 6.74 (d, J = 3.7 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 3.7 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.82 (dd, J = 1.4, 8.6 Hz, 1H), 8.02 (d, J = 1.1 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 9.99 (s, 1H).

5-Formylindole:

5-formyl-N-tosylindole (0.5 g, 1.7 mmol) was dissolved in a mixture of methanol (10 mL) containing 5% aqueous KOH solution (5 mL). The mixture was refluxed for 3 h, neutralized with 1N hydrochloric acid, and extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The residue was purified by short column chromatography to provide 240 mg (97%) of the desired product.

^{1}H NMR ($CDCl_3$) δ 6.70 (t, J = 2.1 Hz, 1H), 7.32 (t, J = 2.3 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 1.5, 8.6 Hz, 1H), 8.19 (s, 1H), 9.45 (b, 1H), 10.15 (s, 1H). GC-MS (pos.): 146.

Ethyl (5-formylindolyl)acetate:

This compound was synthesized according to the general procedure for N-alkylation of indoles.

^{1}H NMR (DMSO-d_6) δ 5.09 (s, 2H), 6.35 (d, J = 2.9 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.97 (s, 1H), 8.48 (s, 1H), 10.93 (s, 1H), 11.58 (s, 1H), 12.90 (brd s, 1H). MS (APCI, neg.): 370.

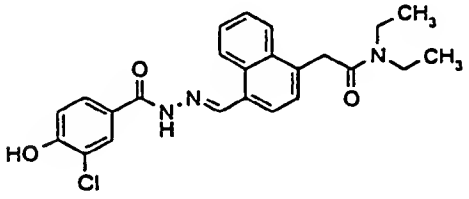
4-[3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthylacetamides and the various indolacetamides (step B):

General library production procedures :

To solutions of 4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]naphthylacetic acid and the various indolylacetic acids in DMSO was added carbonyldiimidazole (1.2 eq). The solution was agitated for 5 minutes and diluted with DMSO to a concentration of 50 mM. The solution was then dispensed into 88 deep well plates containing solutions of amines in DMSO (50 mM). The plates were covered and agitated for 16 hours. The products were purified by HPLC.

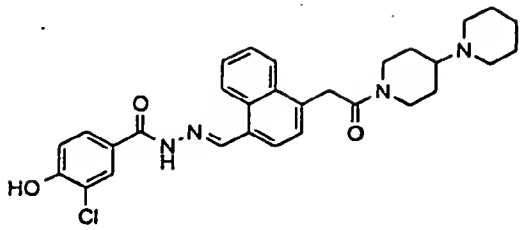
Examples of compounds of the formula XII:

EXAMPLE 343:



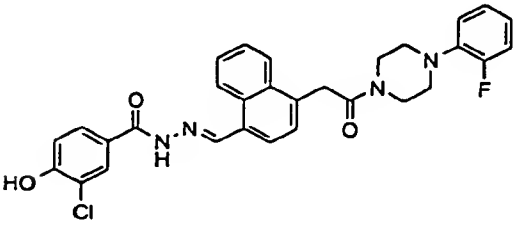
^{1}H NMR (DMSO-D_6): δ 1.06 (t, 3H), 1.17 (t, 3H), 3.31 (qt, 2H), 3.50 (qt, 2H), 4.19 (s, 2H), 7.10 (d, 1H), 7.45 (d, 1H), 7.64 (quintet, 2H), 7.83 (d, 1H), 7.88 (d, 1H), 7.98 (m, 2H), 8.87 (d, 1H), 9.09 (s, 1H), 10.99 (brd s, 1H), 11.80 (brd s, 1H); ms (APCI); 438.1, 440.1.

EXAMPLE 347:



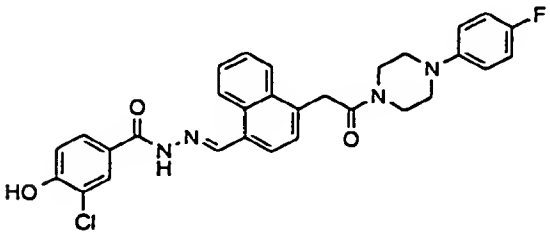
^{1}H NMR (DMSO-D_6): δ 1.26 (m, 2H), 1.37 (m, 4H), 1.67 (m, 2H), 2.43 (m, 4H), 2.62 (m, 3H), 3.10 (t, 2H), 3.90 (d, 1H), 4.32 (s, 2H), 4.48 (d, 1H), 7.10 (d, 1H), 7.31 (d, 1H), 7.48 (m, 2H), 7.81 (d, 1H), 7.88 (d, 1H), 8.03 (m, 2H), 8.85 (d, 1H), 9.08 (brd s, 1H), 11.76 (brd s, 1H): MS (APCI): 533.2.

EXAMPLE 348:

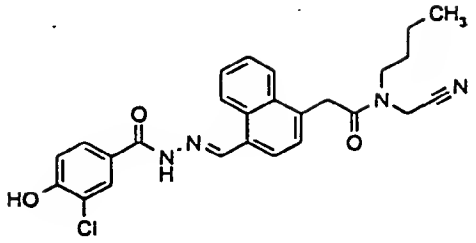


^{1}H NMR (DMSO-D_6): δ 3.03 (m, 4H), 3.68 (t, 2H), 3.79 (t, 2H), 4.30 (s, 2H), 7.14 (m, 5H), 7.47 (d, 1H), 7.66 (quintet, 2H), 7.82 (d, 1H), 7.88 (d, 1H), 8.02 (d, 1H), 8.07 (d, 1H), 8.87 (d, 1H), 9.10 (s, 1H), 10.99 (s, 1H), 11.80 (s, 1H); MS (ACPI): 545.6.

EXAMPLE 349:

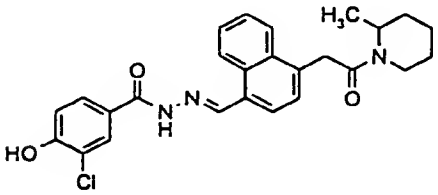


EXAMPLE 352:



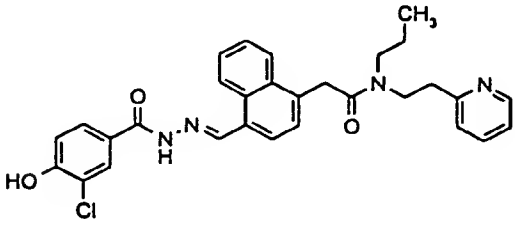
^{1}H NMR (DMSO-D_6): δ 0.9 (t, 3H), 1.30 (sextet, 2H), 1.54 (sextet, 2H), 3.56 (t, 2H), 4.31 (s, 2H), 4.39 (s, 2H), 7.06 (d, 1H) 7.48 (d, 1H), 7.65 (quintet, 2H), 7.79 (dd, 1H), 7.87 (d, 1H), 7.97 (d, 1H), 8.01 (d, 1H), 8.85 (d, 1H), 9.09 (s, 1H), 11.79 (s, 1H); MS (APCI): 477.01, 479.2.

EXAMPLE 353:



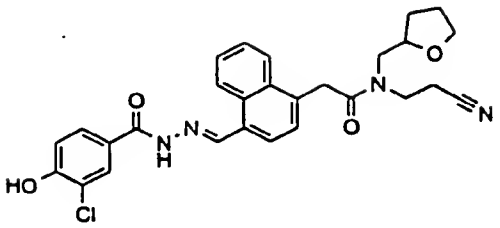
^{1}H NMR (DMSO-D_6): δ 1.17 (m, 4H), 1.54 (m, 4H), 2.68 (m, 1H), 3.77 (d, 1H), 4.18 (s, 2H), 4.33 (m, 1H), 4.76 (brd, 1H), 7.10 (d, 1H), 7.43 (m, 1H), 7.65 (quintet, 2H), 7.81 (d, 1H), 7.88 (d, 1H), 8.02 (s, 1H), 8.04 (d, 1H), 8.84 (d, 1H), 9.09 (s, 1H), 11.79 (s, 1H); MS (APCI): 464.1, 466.2.

EXAMPLE 354:



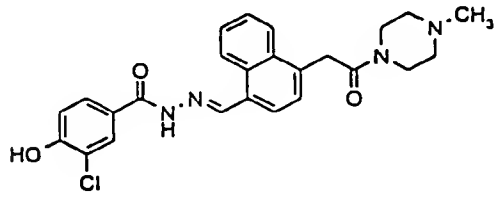
^{1}H NMR (DMSO-D_6): δ 0.85 (qt, 3H), 1.53 (m, 2H), 3.00 (dt, 2H), 3.29 (quintet, 2H), 3.77 (dt, 2H), 4.13 (d, 2H), 7.05 (d, 1H), 7.26 (m, 2H), 7.36 (d, 1H), 7.52 (qt, 1H), 7.69 (m, 2H), 7.87

EXAMPLE 357:



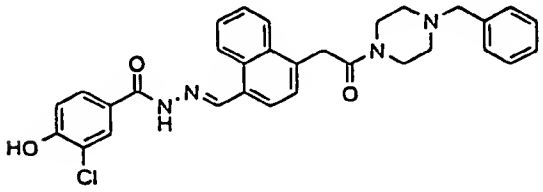
^{1}H NMR (DMSO-D_6): δ 1.50 (m, 1H), 1.90 (m, 2H), 1.95 (m, 1H), 2.72 (t, 1H), 2.95 (t, 1H), 3.30 (m, 1H), 3.55 (m, 1H), 3.65 (t, 2H), 3.75 (m, 1H), 3.92 (t, 1H), 4.12 (t, 1H) 4.35 (d, 2H), 7.11 (d, 1H), 7.48 (m, 1H), 7.65 (t, 1H), 7.68 (t, 1H), 7.8 (dd, 1H), 7.87 (d, 1H), 8.00 (d, 1H), 8.03 (d, 1H), 8.83 (d, 1H), 9.10 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 519.5, 521.2, 522.2.

EXAMPLE 358:



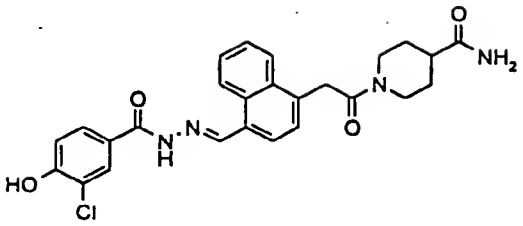
^{1}H NMR (DMSO-D_6): δ 2.19 (s, 3H), 2.30 (m, 4 H), 3.50 (T, 2H), 3.58 (T, 2H), 4.22 (S, 2H), 7.03 (D, 1H), 7.43 (D, 1H), 7.64 (quint, 2H) 7.77 (dd, 1H), 7.87 (d, 1H), 7.99 (d, 1H), 8.04 (s, 1H), 8.83 (d, 1H), 9.09 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 465.2, 467.3.

EXAMPLE 359:



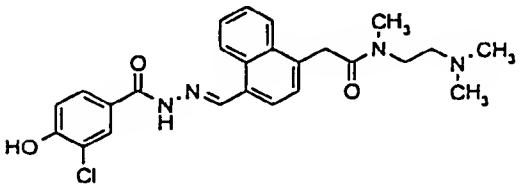
^{1}H NMR (DMSO-D_6): δ 2.38 (m, 4H), 3.51 (s, 4H), 3.61 (t, 2H), 4.22 (s, 2H), 7.08 (d, 1H), 7.31 (m, 5H), 7.43 (d, 1H), 7.61 (quintet, 2H), 7.82 (dd, 1H), 7.88 (d, 1H), 8.00 (s, 1H), 8.02 (d, 1H), 8.85 (d, 1H), 9.10 (s, 1H), 11.80 (brd s, 1H); MS (APCI): 541.4, 543.1.

EXAMPLE 363:



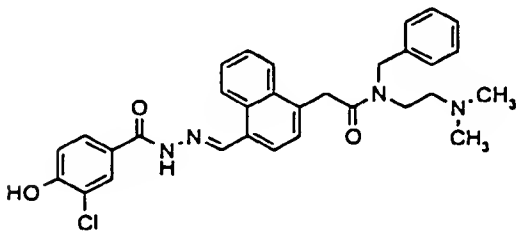
^{1}H NMR (DMSO-D_6): δ 1.50 (m, 2H), 1.68, (d, 2H), 2.28 (t, 1H), 2.59 (t, 1H), 3.05 (t, 1H), 3.96 (d, 1H), 4.16 (s, 2H), 4.32 (d, 1H), 6.74 (brd s, 1H), 6.95 (d, 1H), 7.22 (brd s, 1H), 7.36 (d, 1H), 7.57 (quintet, 2H), 7.71 (dd, 1H), 7.79 (d, 1H), 7.92 (dd, 1H), 7.96 (d, 1H), 8.76 (d, 1H), 9.01 (s, 1H), 11.80 (brd s, 1H); MS (ACPI): 493.1, 495.2.

EXAMPLE 364:

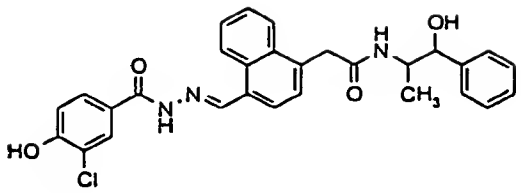


^{1}H NMR (DMSO-D_6): δ 2.10 (s, 3H), 2.15 (s, 3H), 2.29 (t, 1H), 2.40 (t, 1H), 2.80 (s, 1H), 3.05 (s, 2H), 3.36 (t, 1H), 3.46 (t, 1H), 4.16 (d, 2H), 7.01 (d, 1H), 7.38 (t, 1H), 7.56 (m, 2H), 7.72 (dd, 1H), 7.79 (d, 1H), 7.94 (m, 2H), 8.77 (d, 1H), 9.02 (s, 1H), 11.71 (brd s, 1H); MS (ACPI): 467.3, 469.1.

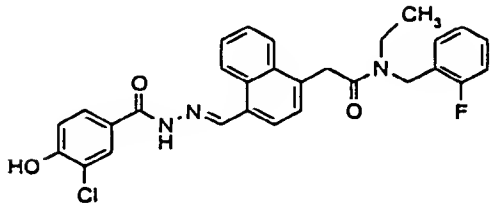
EXAMPLE 365:



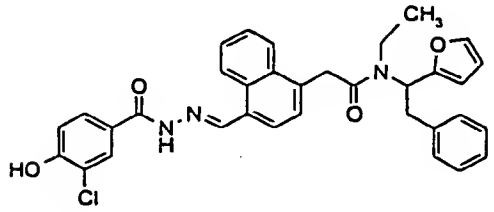
EXAMPLE 366:



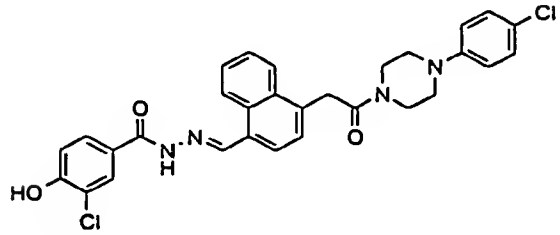
EXAMPLE 367:



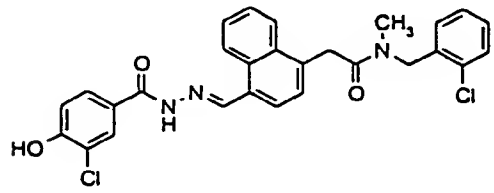
EXAMPLE 368:



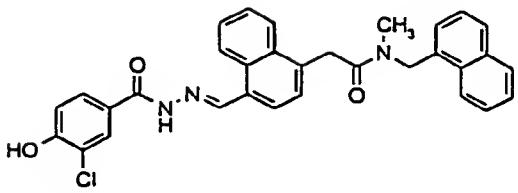
EXAMPLE 369:



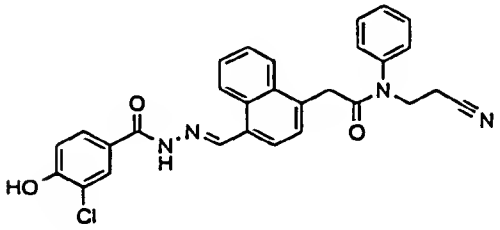
EXAMPLE 370:



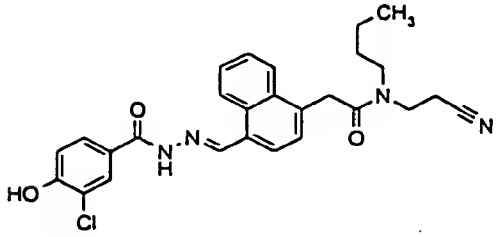
EXAMPLE 371:



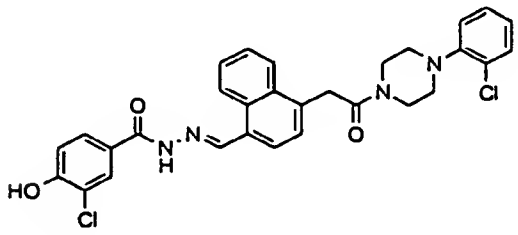
EXAMPLE 372:



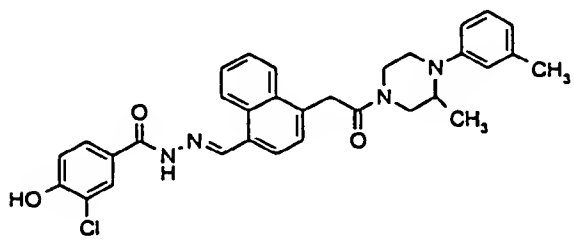
EXAMPLE 373:



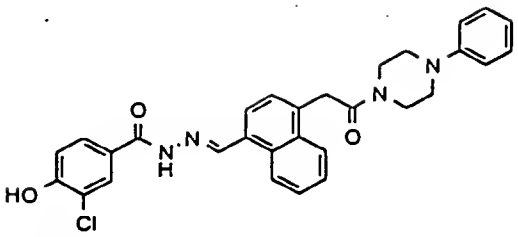
EXAMPLE 374:



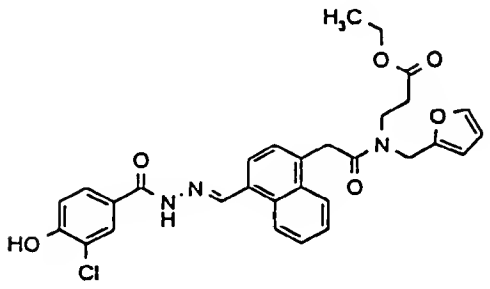
EXAMPLE 375:



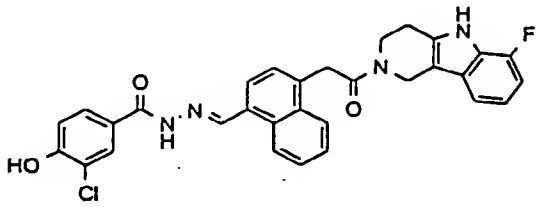
EXAMPLE 386:



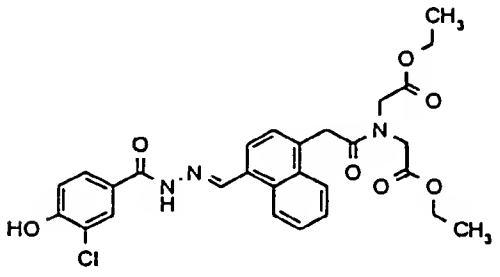
EXAMPLE 387:



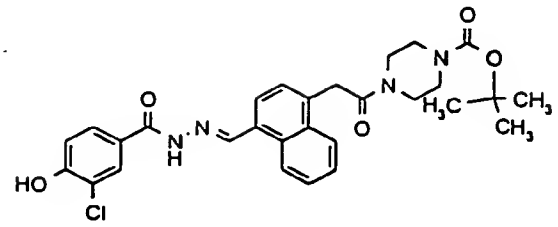
EXAMPLE 388:



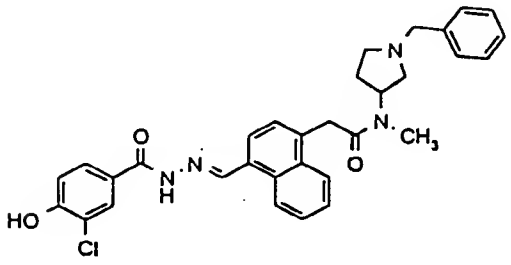
EXAMPLE 389:



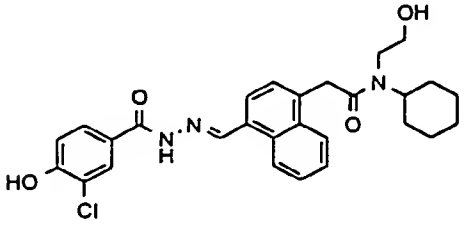
EXAMPLE 390:



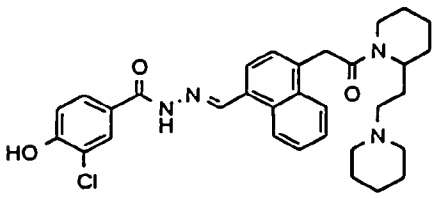
EXAMPLE 391:



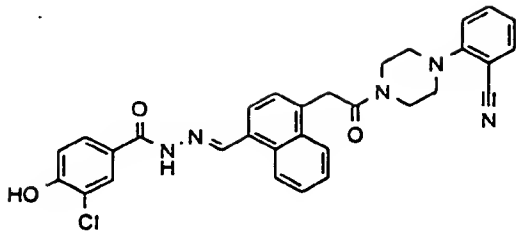
EXAMPLE 392:



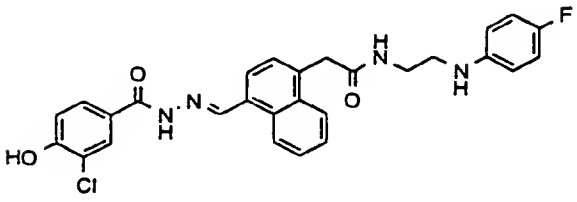
EXAMPLE 393:



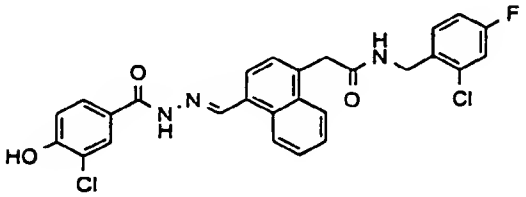
EXAMPLE 402:



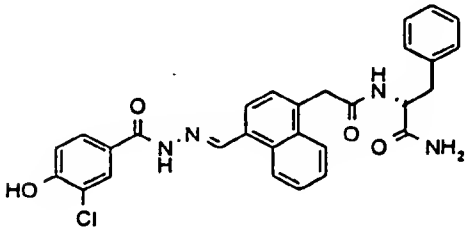
EXAMPLE 403:



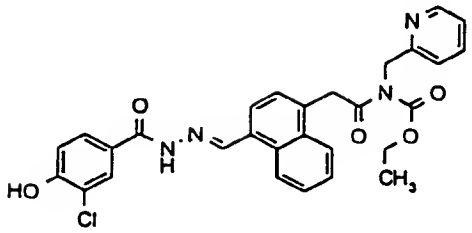
EXAMPLE 404:



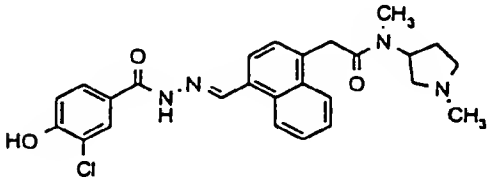
EXAMPLE 405:



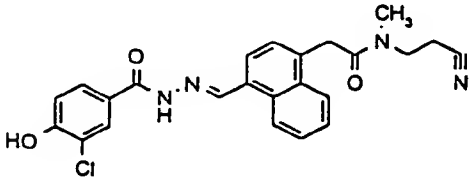
EXAMPLE 406:



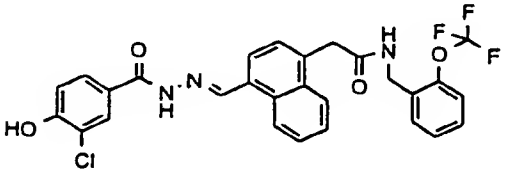
EXAMPLE 407:



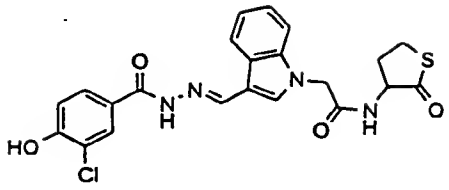
EXAMPLE 408:



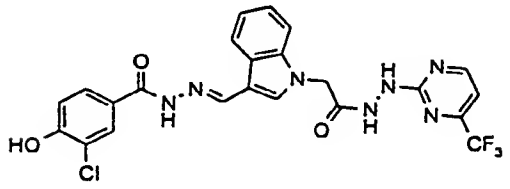
EXAMPLE 409:



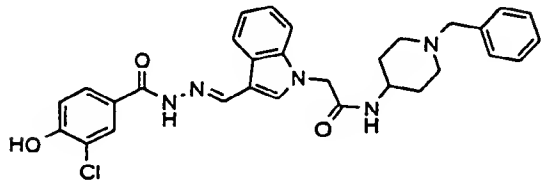
EXAMPLE 420:



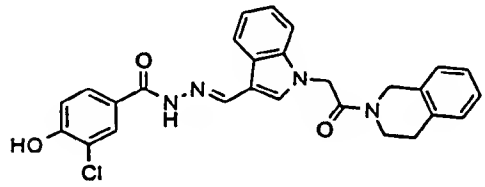
EXAMPLE 421:



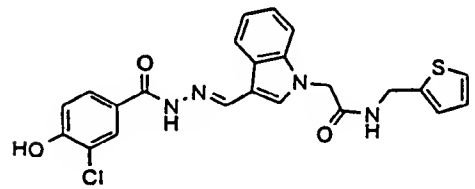
EXAMPLE 422:



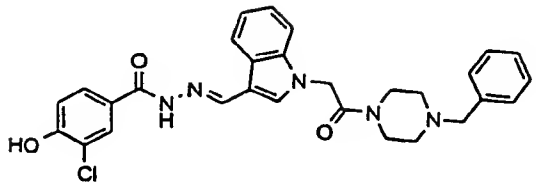
EXAMPLE 423:



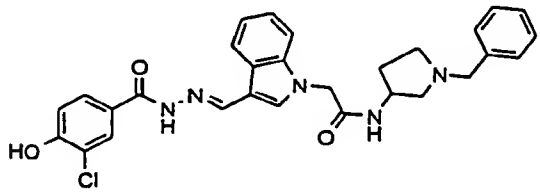
EXAMPLE 424:



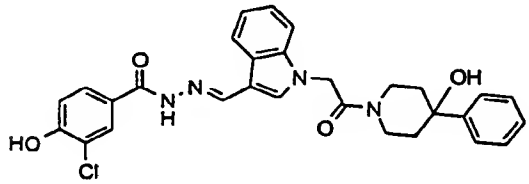
EXAMPLE 425:



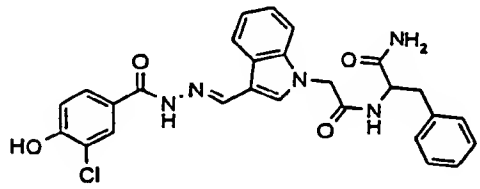
EXAMPLE 426:



EXAMPLE 427:



EXAMPLE 428:



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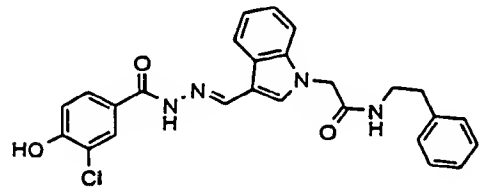

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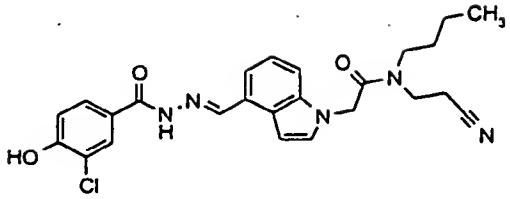
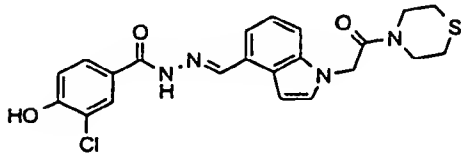
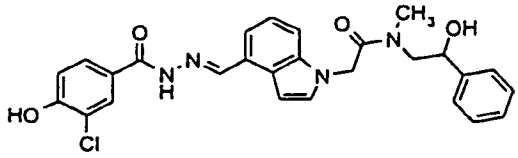


EXAMPLE 440:



EXAMPLE 441:



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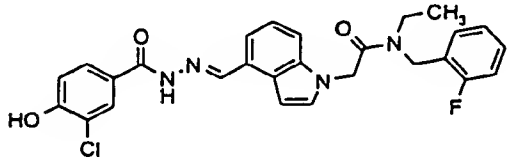
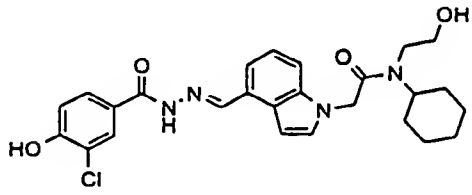


EXAMPLE 443:



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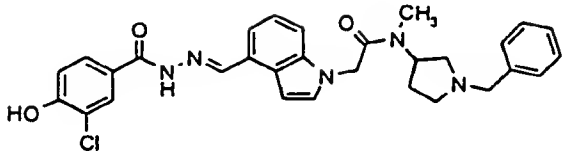

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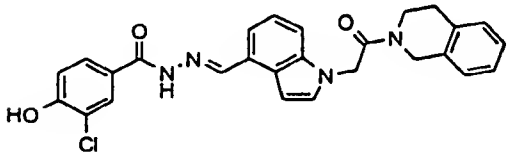
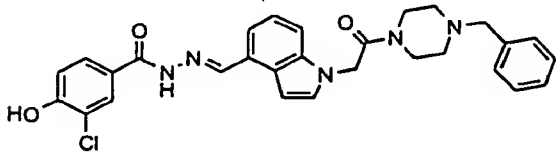
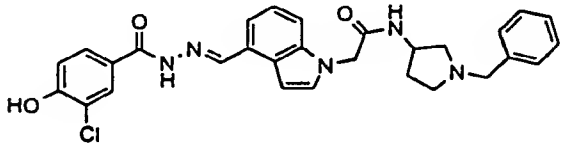


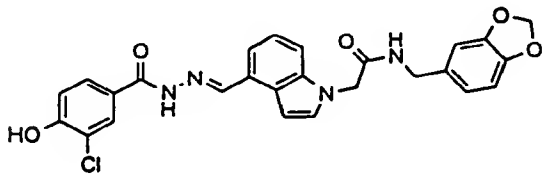
EXAMPLE 446:



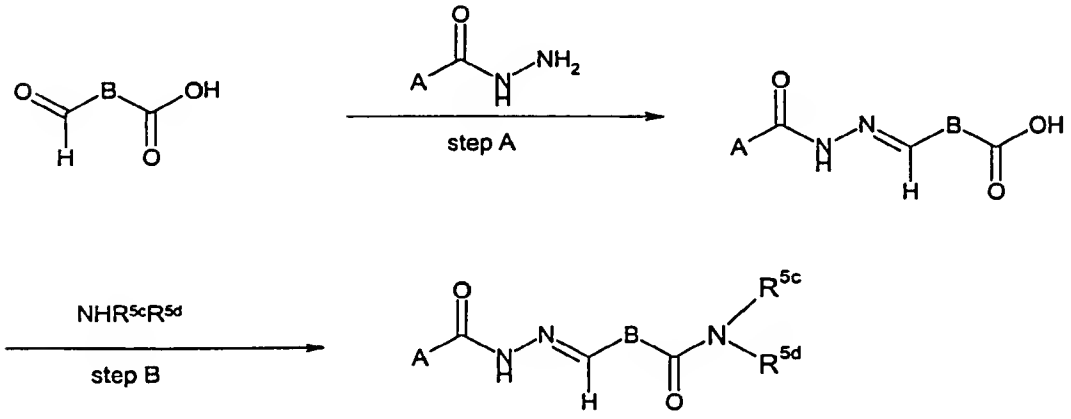
EXAMPLE 447:



EXAMPLE 448:

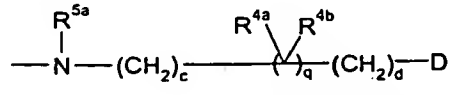


General procedure for synthesis of compounds of the general formula XIII:



formula XIII

A and B are as defined for formula I and $-NR^{5c}R^{5d}$ is

 where R^{5a}, R^{4a}, R^{4b}, c, q, d and D are as defined for formula I or -D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

centrated and dissolved in ethyl acetate. The organic layer was washed with water, brine and dried over $MgSO_4$. Evaporation of the solvent gave the desired product (16 g, 80%).

^1H NMR (DMSO-D_6): δ 5.24 (s, 2H), 7.73 (m, 3H), 8.03 (d, 1H), 8.28 (d, 1H), 8.86 (d, 1H), 13.29 (brd s, 1H).

4-Hydroxymethylnaphthoic acid:

4-Bromomethylnaphthoic acid (16 g, 60 mmol) in an aqueous solution of K_2CO_3 (10%, 100 mL) was stirred at 70 °C for 30 minutes. The reaction mixture was cooled and made acidic with conc. HCl. The resulting precipitate was filtered and dried to give the desired product as a yellow solid in quantitative yield.

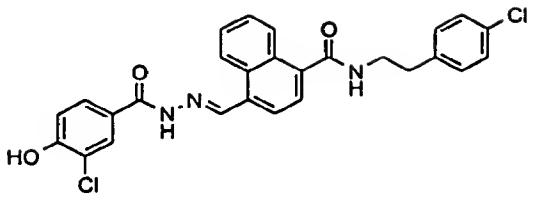
^1H NMR (DMSO-D_6) ; δ 5.01 (s, 2H), 5.96 (s, 1H), 7.70 (m, 3H), 8.10 (m, 2H), 8.90 (d, 1H).

Methyl 4-hydroxymethylnaphthoate:
A mixture of 4-hydroxymethylnaphthoic acid (10 g, 50 mmol), methanol (300 mL), and conc. H_2SO_4 (2 mL) was refluxed overnight. The insolubles were filtered off and the filtrate was concentrated. The residue was taken up in ethyl acetate and washed with aqueous $NaHCO_3$ (2x), brine, dried over $MgSO_4$, and concentrated to give a yellow oil. Silica gel column chromatography using ethyl acetate/hexane (1/3) gave the desired product as a yellow oil (3.3 g, 35%).

^1H NMR ($CDCl_3$): δ 2.05 (t, 1H), 4.01 (s, 3H), 5.22 (s, 2H), 7.66 (m, 3H), 8.09 (d, 1H), 8.16 (d, 1H), 8.96 (d, 1H).

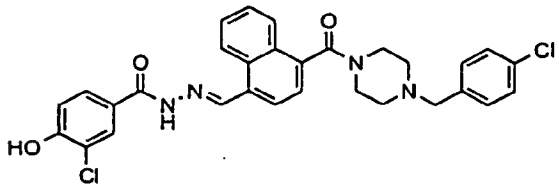
Methyl 4-formylnaphthoate:
To a solution of methyl 4-hydroxymethylnaphthoate above (3.3 g, 15.3 mmol) in dichloromethane (20 mL) was added MnO_2 (6.6 g, 76 mmol). After stirring the dark mixture for 16 hours, the insolubles were filtered through a bed of Celite. Evaporation of the solvent gave the desired product as a white solid in quantitative yield.

EXAMPLE 455:



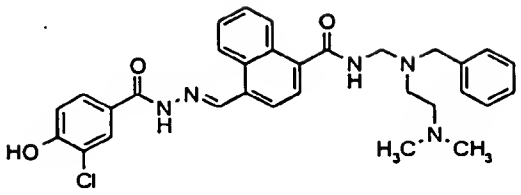
^{1}H NMR (DMSO-D_6): δ 2.91 (t, 2H), 3.67 (t, 2H), 7.12 (d, 1H), 7.38 (qt, 4H), 7.58 (t, 2H), 7.70 (t, 1H), 7.50 (d, 1H), 7.95 (d, 2H), 8.03 (s, 1H), 8.69 (brd t. 1H), 8.81 (d. 1H), 9.12 (s, 1H), 11.02 (s, 1H), 11.89 (s, 1H); MS (APCI): 507.3, 508.5.

EXAMPLE 456:

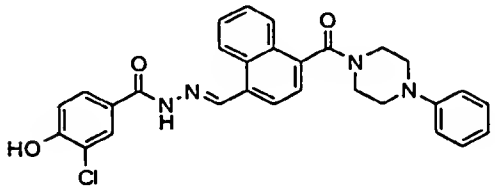


^{1}H NMR (DMSO-D_6): δ 2.20 (brd m, 1H), 2.30 (brd m, 1H), 2.55 (m, 2H), 3.10 (brd m, 2H), 3.50 (s, 2H), 3.72 (brd m, 1H), 3.85 (brd m, 1H), 7.10 (d, 1H), 7.36 (qt, 4H), 7.53 (d, 1H), 7.70 (m, 2H); 7.82 (m, 2H), 7.95 (d, 1H), 8.03 (s, 1H), 8.88 (d, 1H), 9.11 (s, 1H), 11.00 (brd s, 1H), 11.89 (s, 1H); MS (APCI, neg.): 559.2, 561.2.

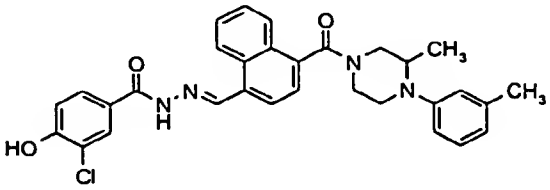
EXAMPLE 467:



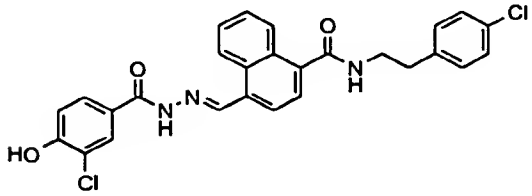
EXAMPLE 468:



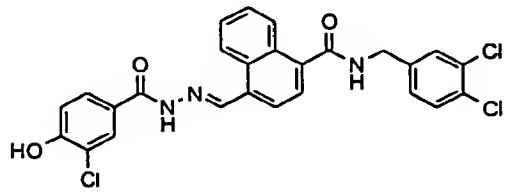
EXAMPLE 469:



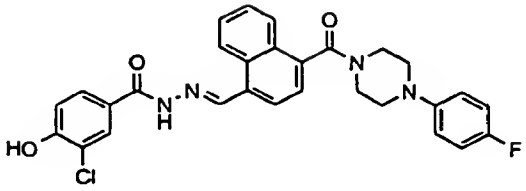
EXAMPLE 470:



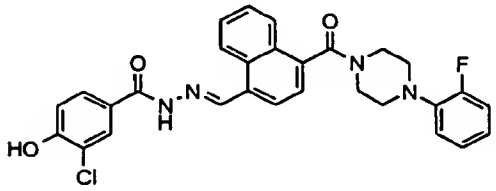
EXAMPLE 471:



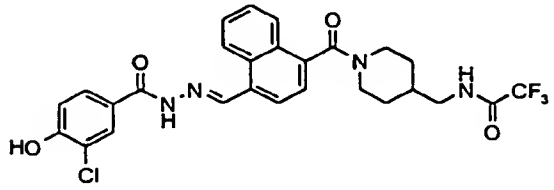
EXAMPLE 472:



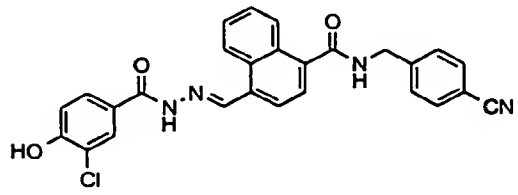
EXAMPLE 473:



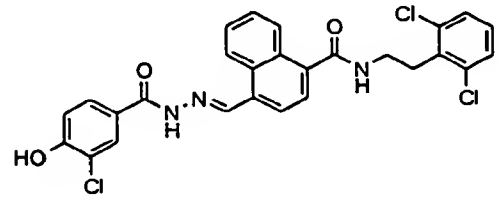
EXAMPLE 474:



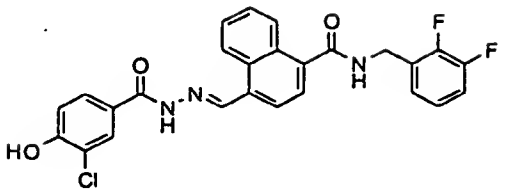
EXAMPLE 475:



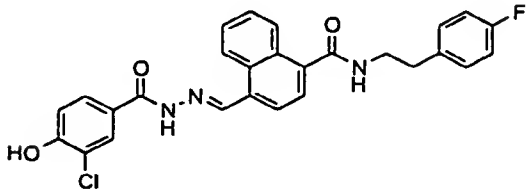
EXAMPLE 476:



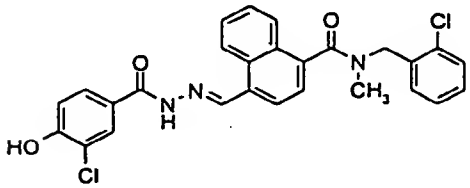
EXAMPLE 487:



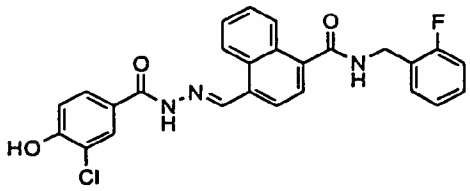
EXAMPLE 488:



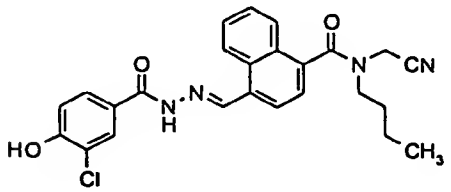
EXAMPLE 489:



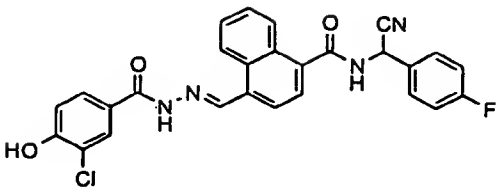
EXAMPLE 490:



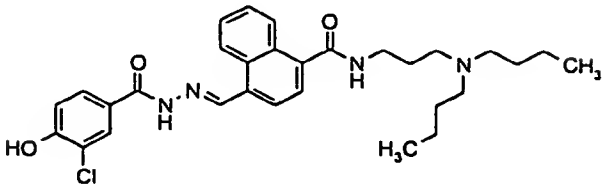
EXAMPLE 491:



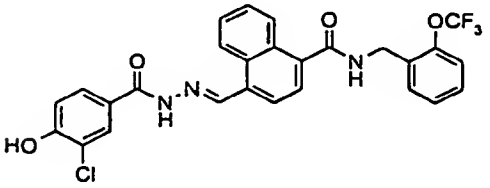
EXAMPLE 492:



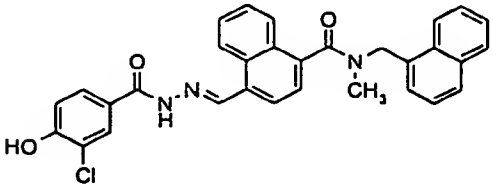
EXAMPLE 493:



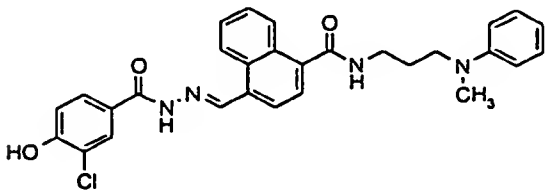
EXAMPLE 494:



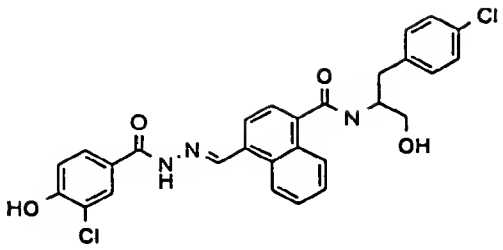
EXAMPLE 495:



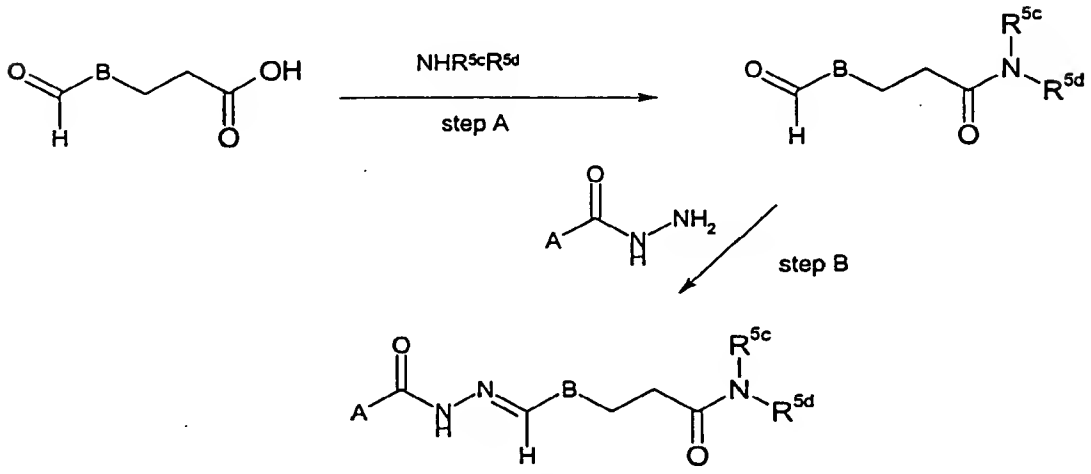
EXAMPLE 496:



EXAMPLE 507:

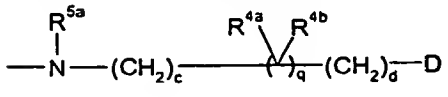


General procedure for synthesis of compounds of the general formula XIV:



formula XIV

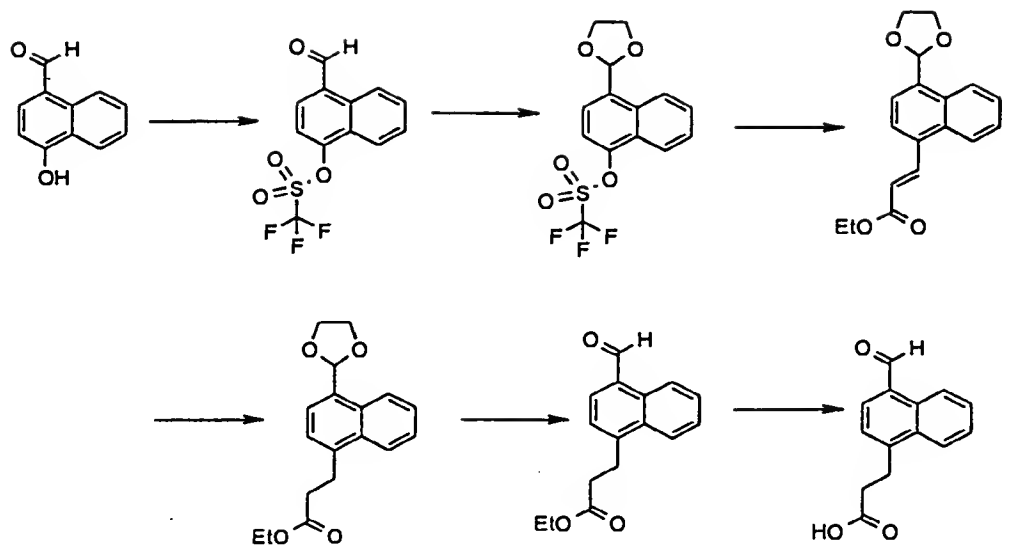
A and B are as defined for formula I and $-NR^{5c}R^{5d}$ is



where R^{5a}, R^{4a}, R^{4b}, c, q, d and D are as defined for formula I or

-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step A: The acid is coupled to a primary or secondary amine using one of the methods well-known to those skilled in the art. This coupling can be performed using one of the standard amide or peptide synthesis procedures such as by generating an active ester, an anhydride or



4-Trifluoromethylsulfonyloxy naphthaldehyde:

To a solution of 4-hydroxy naphthaldehyde (34.4 g, 0.20 mol) in dichloromethane (200 mL) and pyridine (19 mL, 18.58 g, 0.23 mol) was added dropwise at 0°C trifluoromethane sulfonic anhydride (46.75 g, 0.16 mol). The mixture was stirred at 0°C for 2 hr and at room temperature for 16 hr. It was poured into water (200 mL), and extracted with ether (3 x 100 mL). The combined organic extracts were washed with water (100 mL), 0.1 N hydrochloric acid (2 x 100 mL), water (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated.

^1H NMR ($CDCl_3$) δ 7.89 - 7.97 (m, 3H), 8.09 (dd, J = 2.8, 6.5 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 9.24 (dd, J = 2.8, 6.5 Hz, 1H), 10.45 (s, 1H).

2-(4-Trifluoromethylsulfonyloxy naphthyl) dioxolane:

A solution of 4-trifluoromethylsulfonyloxy naphthaldehyde (4.09 g, 13.4 mmol), ethylene glycol (1.5 mL, 1.67 g, 26.9 mmol), and p-toluene sulfonic acid (250 mg) in toluene (250 mL) was refluxed for 16 hr using a Dean -Stark trap. The solution was allowed to reach room temperature, was washed with satd. $NaHCO_3$-sol. (2x 80 mL), brine (80 mL), dried ($MgSO_4$), and concentrated to give a yellow oil (4.79 g, quant).

^1H NMR ($CDCl_3$) δ 4.19 (m, 4H), 6.47 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.66- 7.70 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 8.13 (dd, J = 3.3, 6.3 Hz, 1H), 8.30 (dd, J = 3.3, 6.3 Hz, 1H).

3-(4-formylnaphthalene)propanoic acid:

Ethyl 3-(4-formylnaphthalene)propanoic acid (310 mg, 1.2 mmol) was suspended in water (10 mL), and Na_2CO_3 (130 mg, 1.2 mmol) was added. The mixture was refluxed for 5 hr, and allowed to cool to room temperature. After acidification with conc. hydrochloric acid, a precipitate was formed. The precipitate was collected by suction, and dried at 80°C in vacuum for 16 hr to give a white solid (300 mg, 73%).

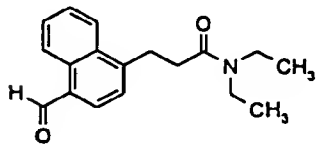
^{1}H NMR (DMSO-D_6) δ 2.69 (t, J = 7.0 Hz, 2H), 3.39 (t, J = 7.0 Hz, 2H), 7.66-7.77 (m, 2H), 8.10 (d, J = 7.3 Hz, 1H), 8.23 (dd, J = 1.1, 8.0 Hz, 1H), 9.22 (dd, J = 1.1 , 9.0 Hz, 1H), 10.33 (s, 1H), 12.30 (br s, 1H).

General procedure (Step A):

Preparation of 3-(4-formylnaphthalene)propanamides:

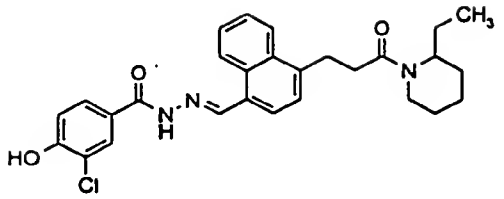
To a solution of 3-(4-formylnaphthalene)propanoic acid (100 mg, 0.437 mmol) in DMF (3 mL) was added carbonyl diimidazole (140 mg, 0.863 mmol). The mixture was stirred at room temperature for 1 hr, and amine (1.3 equivalents) was added. After stirring at room temperature for 16 hr, the mixture was diluted with ethylacetate (5 mL), extracted with water (5 mL), 1 N hydrochloric acid (5 mL), and water (3 x 5 mL), dried ($MgSO_4$) and concentrated. After flash chromatography using hexane/ethylacetate 1 : 1 pure amide was isolated.

Examples of amides:



^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.0 Hz, 3H),1.12 (t, J = 7.0 Hz, 3H), 2.79 (t, J = 8.0 Hz, 2H), 3.50 (t, J = 8.0 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1 H), 7.64 - 7.71 (m, 2H), 7.92 (d, J = 7.3 Hz, 1H), 8.18 (dd, J = 1.3, 8.0 Hz, 1H), 9.34 (dd, J = 1.3, 8.0 Hz, 1H), 10.34 (s, 1H). MS (APCI, pos.) 284.1

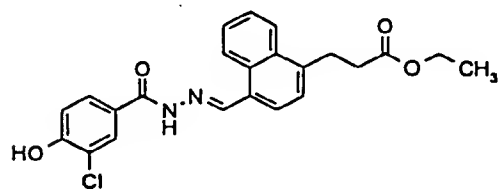
EXAMPLE 509:



^{1}H NMR (DMSO-D_6) δ 0.68 (t, J = 7.5 Hz, 3H), 0.75 (t, J = 7.5 Hz, 3H), 0.76 (dd, 0.5 H), 0.90 (dd, 0.5 H), 1.02 - 1.68 (m, 8H), 2.49 (m. 0.5H), 2.75 (m, 2H), 2.90 (t, J = 14.0 Hz, 0.5H), 3.33 (m, 2H), 3.61 (d, J = 12.0, Hz, 0.5H), 3.75 (m, 0.5H), 4.36 (d, J = 12.0 Hz, 0.5H), 4.53 (m, 0.5H), 7.08 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.64 - 7.66 (m, 2H), 7.80 (dd, J = 1.9, 8.5 Hz, 1), 7.83 (d, J =7.5 Hz, 1H), 8.00 (d, J = 1.9, Hz, 1H), 8.17 (m, 1H), 8.88 (d, J = 7.5 Hz, H), 7.25 (s, 1H), 11.0 (s, 1H), 11.76 (s, 1H). MS (APCI, pos.): 492.1, 494.1

EXAMPLE 510:

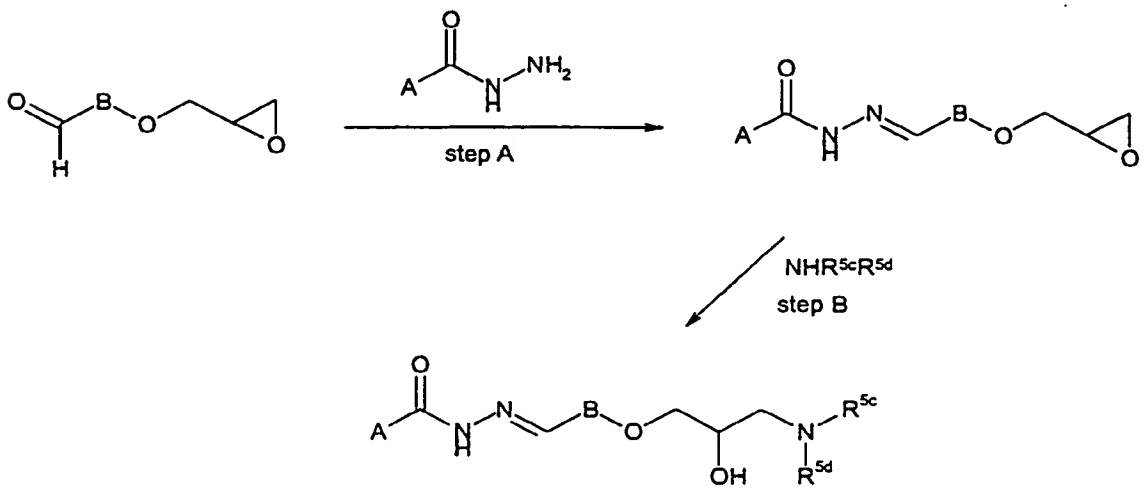
Ethyl 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl propanate



The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of ethyl 4-formyl-1-naphthylpropanate (from step E) and 3-chloro-4-hydroxy benzoic acid hydrazide.

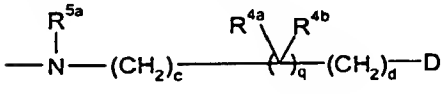
^{1}H NMR (DMSO-D_6) δ 1.14 (t, J = 7.0 Hz, 3H), 2.73 (t, J = 7.5 Hz, 2H), 3.35 (t, J = 7.5 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 7.08 (d, J = 8.6 Hz, 1H), 7.66 (m, 2H), 7.79 (dd, J = 1.8, 8.6 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 8.85 (d, J = 7.7 Hz, 1H), 9.05 (s, 1H), 11.0 (brd s, 1H), 11.78 (s, 1H). MS (APCI, pos.): 425.5, 427.3

General procedure for synthesis of compounds of the general formula XV:



formula XV

A and B are as defined for formula I and $-NR^{5c}R^{5d}$ is

 where R^{5a}, R^{4a}, R^{4b}, c, q, d and D are as defined for formula I or -D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

Step A: The carbonyl compounds are treated with an acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, DMSO, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column

mL) was added. The mixture was extracted with ethyl acetate (3x80 mL), dried ($MgSO_4$), and concentrated to give a brown solid (1.23 g, 93%).

^1H NMR ($CDCl_3$) δ 2.88 (dd, J = 2.6, 4.8 Hz, 1H), 3.02 (dd, J = 4.0, 4.6 Hz, 1H), 3.51 - 3.57 (m, 1H), 4.22 (dd, J = 5.8, 11.1 Hz, 1H), 4.55 (dd, J = 2.8, 11.1 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 9.31 (d, J = 8.6 Hz, 1H), 10.22 (s, 1H).

General Procedure:

4-hydroxybenzoic acid 4-(2,3-epoxypropanoxy)-1-naphthylidene hydrazide derivatives (step A):

The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the above epoxy-aldehyde with 4-hydroxy benzoic acid hydrazide derivatives.

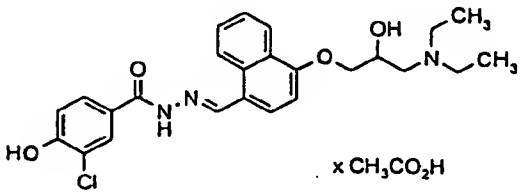
^1H NMR (DMSO-d_6) δ 2.84 (dd, J = 2.2, 4.9 Hz, 1H), 2.92 (dd, J = 4.5, 4.5 Hz, 1H), 3.45 - 3.57 (m, 1H), 4.11 (dd, J = 6.4, 11.3 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 7.02 - 7.18 (m, 2H), 7.55 - 7.90 (m, 4H), 7.99 (d, J = 1.9 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.90 - 9.05 (d, 2H), 10.94 (s, 1H), 11.66 (s, 1H). MS (APCI, negative): 395.

General procedure for epoxide ring opening (step B):

A mixture of epoxide (0.2 mmol) and amine (0.3 mmol) in 10 mL ethanol was refluxed for 4 hr. A red oil was obtained after concentration. Products were purified by preparatory HPLC.

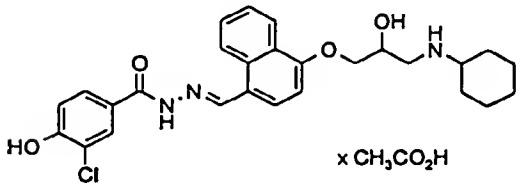
Examples of compounds of formula XV:

EXAMPLE 512:



^{1}H NMR (DMSO-d_6) δ 1.25 -1.82 (m, 8H), 1.88 (s, 3H), 2.68 -2.90 (m, 2H), 3.08 (m, 1H), 4.0 - 4.25 (m, 3H), 7.03 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.52 - 7.85 (m, 4H), 7.97 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.85 - 9.0 (d, 2H), 11.61 (s, 1H); MS (APCI, pos.): 482.

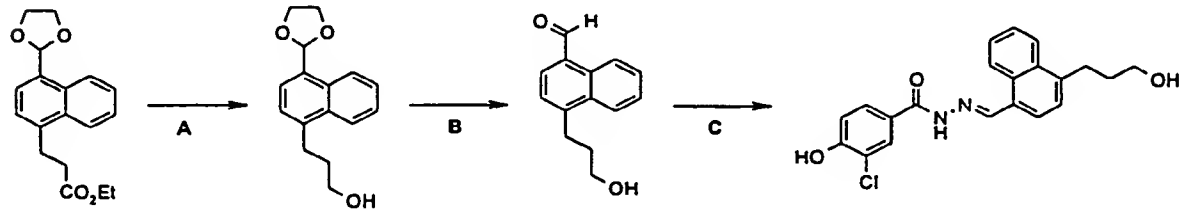
EXAMPLE 516:



^{1}H NMR (DMSO-d_6) δ 0.95 -1.80 (m, 10H), 1.88 (s, 3H), 2.45 (m, 1H), 2.70 -2.90 (m, 2H), 3.98-4.30 (m, 3H), 7.02 (d, J = 8.52 Hz, 1H), 7.07 (d, J = 8.2 Hz, H), 7.52 -- 7.75 (m, 4H), 7.97 (d, J = 2.05 Hz, 1H), 8.34 (d, J = 8.33 Hz, 1H), 8.87 - 9.00 (m, 2H), 11.61 (s, 1H); MS (APCI, pos.): 496.

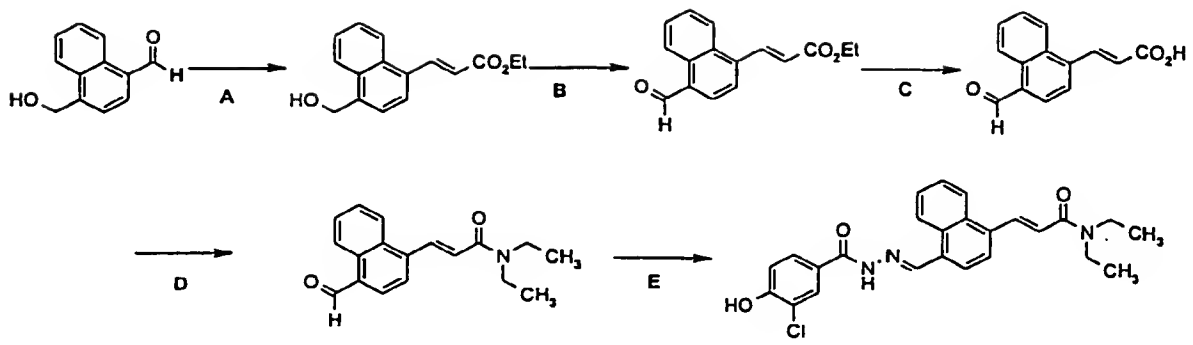
EXAMPLE 517:

3-Chloro-4-hydroxybenzoic acid 4-(3-hydroxypropyl)naphthylmethylene hydrazide



2-[4-(3-Hydroxypropyl)naphthyl]dioxolane (step A):

To a solution of 2-[4-(2-ethoxycarbonylethyl)naphthyl]dioxolane (210 mg, 0.70 mmol) in anhydrous THF (5 mL) was added at 0°C 1M lithium aluminum hydride in THF (0.5 mL). THF (5 mL) was added and the mixture was stirred at room temperature for 16 hr, diluted with water (10 mL), acidified with conc. hydrochloric acid, and extracted with ether (3x 10 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography using hexane/ethyl acetate 2:1 as eluent to provide 67 mg (37 %) of a colorless oil.



Ethyl (4-hydroxymethyl) naphthalene acrylate (step A):

To a suspension of sodium hydride (160 mg, 60% dispersion in mineral oil, 4.00_mmol) in THF (10 mL) at 0°C was added triethylphosphonoacetate (0.77 mL, 670 mg, 3.88 mmol). The mixture was stirred at 0°C for 1 hr, and 4-hydroxymethyl naphthaldehyde (600 mg, 3.2 mmol) in THF (5 mL) was added at the same temperature. The mixture was stirred at room temperature for 16 hr, diluted with satd. NH_4Cl-solution (10 mL), and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated, to provide 900 mg of a colorless oil, which was used without further purification in the next step.

^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 1.86 (brd s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 5.17 (s, 2H), 6.50 (d, J = 15.7 Hz, 1H), 7.54 - 7.62 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 8.13 (dd, J = 2.8, 9.8 Hz, 1H), 8.21 (dd, J = 2.8, 9.8 Hz, 1H), 8.49 (d, J = 15.7 Hz, 1H).

Ethyl 4-formylnaphthalene acrylate (step B):

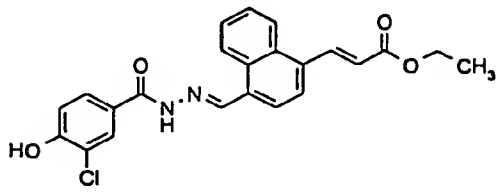
The crude material (900 mg) from step A was dissolved in chloroform (10 mL), and manganese dioxide (1.5 g, 17 mmol) was added. After stirring at room temperature for 16 h, the suspension was filtered by suction through Celite, and the filtrate was concentrated. Flash chromatography using hexane/ethyl acetate 5:1 provided 491 mg (60% over 2 steps) of a colorless oil.

^1H NMR ($CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 1.86 (brd s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 6.60 (d, J = 15.7 Hz, 1H), 7.68 - 7.75 (m, 2H), 7.85 (d, J = 7.4 Hz, 1H), 8.00 (d, J = 7.4 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.50 (d, J = 15.7 Hz, 1H), 9.31 (dd, J = 1.3, 8.1 Hz, 1H), 10.43 (s, 1H). MS (APCI, neg.): 254.1

2.1, 7.2 Hz, 1H), 8.32 (d, J = 15.1 Hz, 1H), 8.83 (d, J = 7.0 Hz, 1H), 9.13 (s, 1H), 11.00 (s, 1H), 11.86 (s, 1H). MS (APCI, pos.): 450.3

EXAMPLE 519:

Ethyl 4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl acrylate

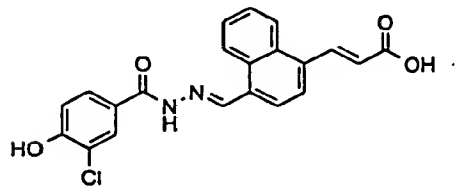


The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of ethyl 4-formyl-1-naphthyl acrylate (from step B) and 3-chloro-4-hydroxy benzoic acid hydrazide.

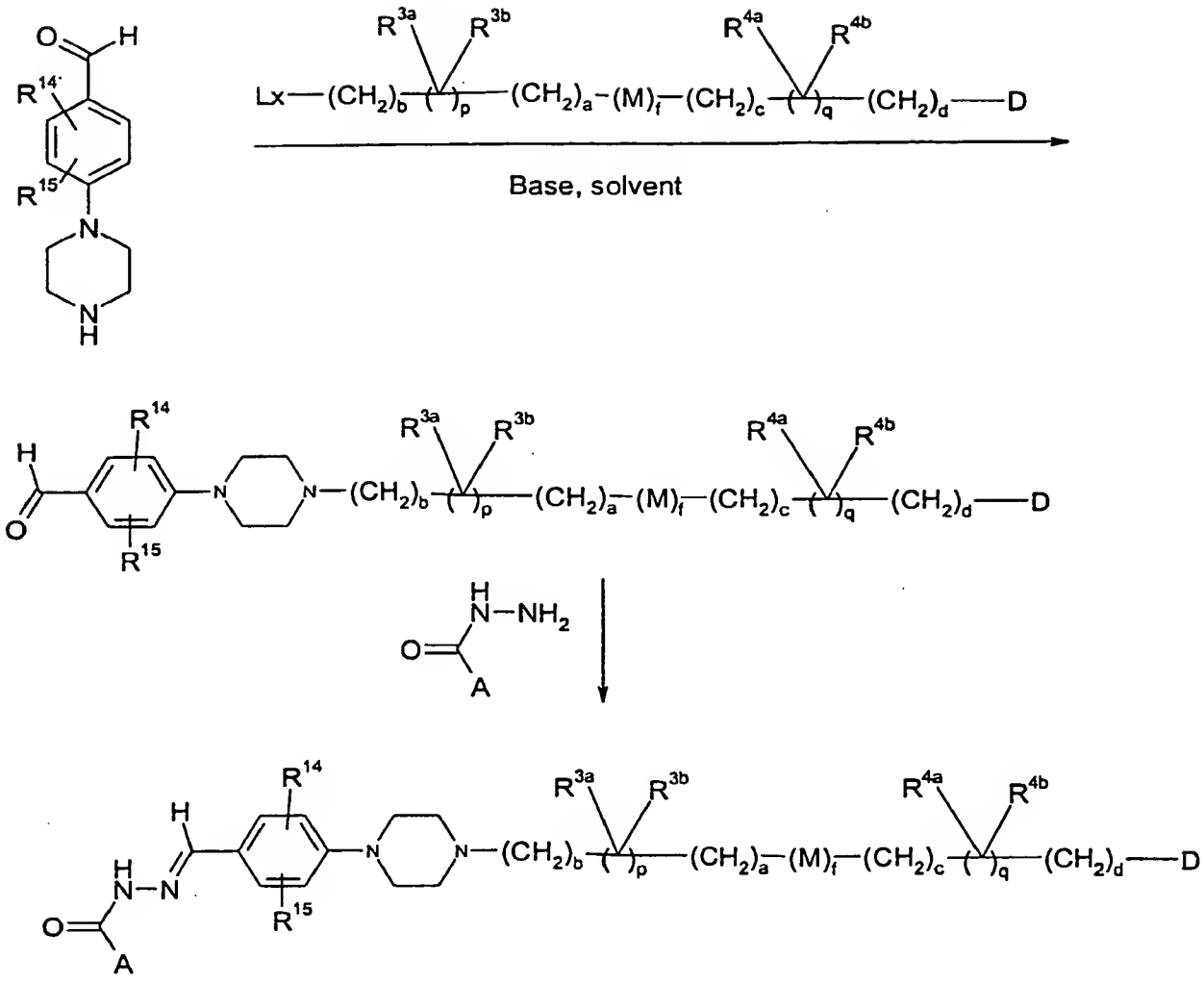
^{1}H NMR (DMSO-D_6) δ 1.29 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 6.75 (d, J 15.7 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.71 (m, 2H), 7.92 (d, J = 8.5 Hz, 1H), 8.01 (m, 2H), 8.07 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 15.7 Hz, 1H), 8.81 (d, J = 7.1 Hz, 1H), 9.13 (s, 1H), 11.00 (s, 1H), 11.89 (s, 1H). MS (APCI, pos.): 421.1, 423.0

EXAMPLE 520:

4-[(3-Chloro-4-hydroxybenzoyl) hydrazonomethyl] naphthyl acrylate



The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl -1-naphthyl acrylate (from step C) and 3-chloro-4-hydroxy benzoic acid hydrazide.



wherein Lx is a leaving group such as -Cl, -Br, -I, $-OSO_2CH_3$, $-OSO_2$p-tolyl or $-OSO_2CF_3$; and A, R^{3a}, R^{3b}, R^{4a}, R^{4b}, a, b, c, d, f, p, q, D, M, R^{14} and R^{15} are as defined for formula I.

According to the above scheme the substituted piperazine-aryl-aldehydes can be prepared by stirring piperazinylbenzaldehydes or piperazinylnaphthaldehydes in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, DMSO, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkyl halide or an aryl-lower alkyl halide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or

al. The excess phosphorous oxychloride was distilled off and the entire mixture was diluted with ethyl acetate and added slowly to 500 mL of ice-chips. The solution was neutralized and made basic with concentrated NaOH. The neutralization and basification must be done at low temperatures to avoid creating by-products. The formylated product was extracted with ethyl acetate (5x). The organic layer was washed with water (2x), brine, dried over magnesium sulfate and purified by silica gel column chromatography using gradient hexane/ethyl acetate (10/0 to 8/2). The product (9 g, 81%) was obtained as an oil.

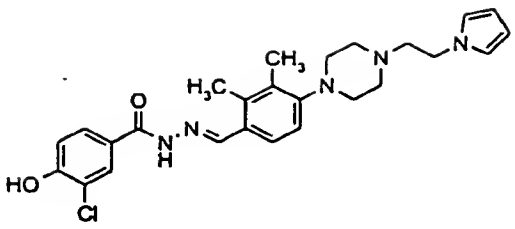
^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.28 (s + t, 7H), 3.03 (t, 4H), 3.59 (s, 2H), 6.75 (s, 1H), 7.31 (m, 5H), 7.58 (s, 1H), 10.12 (s, 1H).

4-(2,5-dimethyl-4-formylphenyl)-1-(1-chloroethoxycarbonyl)piperazine:
The 4-(2,5-dimethyl-4-formylphenyl)-1-benzylpiperazine (9 g, 29 mmol) was dissolved in anhydrous 1,2-dichloroethane (100 mL) and 1-chloroethyl chloroformate (4.5 g, 31.5 mmol) was added. The solution was refluxed for 30 minutes or until TLC analysis indicated the disappearance of the starting material. The product was just slightly less polar than the starting material by TLC using hexane/EtOAc (3/1). Dichloroethane was evaporated and the residue was chromatographed using gradient hexane/EtOAc (10/0 to 8/2) to give the product (6 g, 64%) as an oil.

^{1}H NMR ($CDCl_3$) δ 1.84 (d, 3H), 2.32 (s, 3H), 2.61 (s, 3H), 2.99 (brd m, 4H), 3.70 (brd m, 4H), 6.62 (qt, 1H), 6.76 (s, 1H), 7.62 (s, 1H), 10.14 (s, 1H).

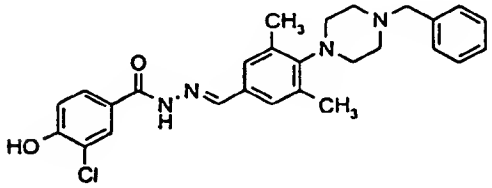
4-piperazinyl-2,5-dimethylbenzaldehyde:
To a solution of the dimethylphenylpiperazinylcarbamate above (6 g, 18.5 mmol) in THF (50 mL) was added 1 N HCl (50 mL, 50 mmol). The mixture was warmed to approximately 80 ^{o}C until the evolution of CO_2 stopped. Most of the THF was removed by rotary evaporation and the residue was lyophilized to give the product as the dihydrochloride salt (5.5 g, 99%).

^{1}H NMR (DMSO-D_6) δ 2.2 (s, 3H), 2.50 (s, 3H), 3.13 (brd s, 8H), 6.85 (s, 1H), 7.54 (s, 1H), 9.49 (brd s, 2H), 10.02 (s, 1H).



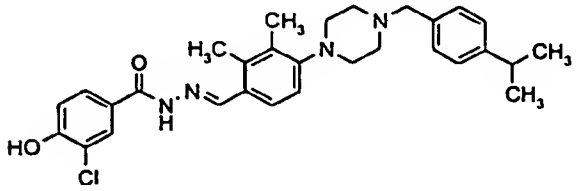
^{1}H NMR (DMSO-D_6): δ 2.26 (s, 3H), 2.38 (s, 3H), 2.65 (brd s, 4H), 2.73 (t, 2H), 2.89 (brd s, 4H), 4.07 (t, 2H), 6.03 (d, 2H), 6.84 (t, 2H), 7.02 (d, 1H), 7.13 (d, 1H), 7.72 (d, 1H), 7.82 (dd, 1H), 8.01 (s, 1H), 8.86 (brd s, 1H), 11.68 (brd s, 1H); MS (APCI): 480.7, 482.3.

EXAMPLE 522:



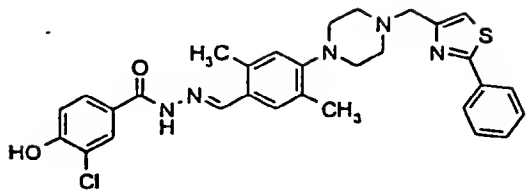
^{1}H NMR (DMSO-D_6): δ 2.49 (s, 6H), 2.68 (brd s 4H), 3.22 (brd s, 4H), 3.72 (s, 2H), 7.22 (d, 1H), 7.44 (m, 1H), 7.52 (m, 6H), 7.92 (dd, 1H), 8.13 (s, 1H), 8.46 (s, 1H), 11.12 (brd s, 1H), 11.80 (s, 1H); MS (APCI): 477.5, 479.2.

EXAMPLE 523:



^{1}H NMR (DMSO-D_6): δ 1.25 (s, 3H), 1.27 (s, 3H), 2.26 (s, 3H), 2.38 (s, 3H), 2.57 (brd s, 4H), 2.95 (brd s, 4H), 3.56 (s, 2H), 7.02 (d, 1H), 7.12 (d, 1H), 7.30 (qt, 4H), 7.72 (d, 1H), 7.82 (d, 1H), 8.01 (s, 1H), 8.83 (s, 1H), 11.0 (brd s, 1H), 11.1 (s, 1H); MS (APCI): 519.7, 521.5.

EXAMPLE 527:



^{1}H NMR (DMSO-D_6): δ 2.21 (s, 3H), 2.37 (s, 3H), 2.66 (brd s, 4H), 2.91 (brd s, 4H), 3.76 (s, 2H), 6.83 (s, 1H), 7.05 (d, 1H), 7.62 (s, 1H), 7.69 (s, 1H), 7.75 (dd, 1H), 7.86 (d, 2H), 7.94 (s, 1H), 8.15 (d, 2H), 8.60 (s, 1H), 10.92 (brd s, 1H), 11.55 (s, 1H); MS (APCI): 628.3, 630.2, 631.2.

General procedure for the synthesis of N-substituted indole aldehydes followed by hydrazone formation:

The N-substituted indole aldehydes may be prepared by N-alkylation of the corresponding unsubstituted indole aldehydes using various electrophilic alkylating agents that introduce the -$(K)_m$-D moiety as defined above.

preferably in an inert atmosphere of N_2 or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture.

The following step, the hydrazone formation is described above in general and below in detail.

Library Procedure for Indole Alkylation (Step A):

Preparation of the sodium salt of the indole:

Indole-3-carboxaldehyde (1.45 g) was dissolved into 8.6 mL of dry DMF in a dried and cooled 3 100 mL 3-necked roundbottom flask.

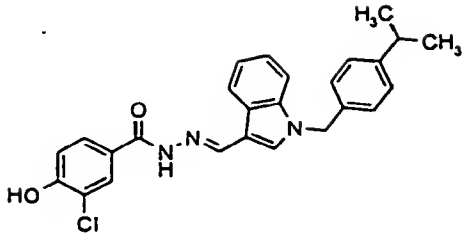
Evolution of large amounts of hydrogen gas occurs during this step. Care should be taken to keep the flow of inert gas steady and maintain adequate venting to accommodate the hydrogen gas evolution.

While maintaining a steady flow of nitrogen or argon through the 3-necked round bottomed flask, 1.1 equivalent of sodium hydride (0.27 g of dry 95% reagent) was transferred to the indole solution. The mixture was stirred for 15 minutes, while maintaining flow of inert gas. Proceeded promptly to the next step.

Preparation of the alkyl halide solutions:

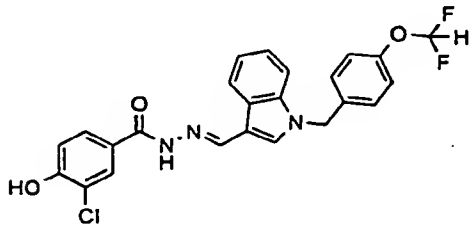
Amber glass vials (for preparing stock solutions) were dried for at least four hours at 110 °C, then were allowed to cool under an argon atmosphere in a desiccator. Alkyl halides solutions (1.0 M) were prepared in anhydrous DMF in the dried vials. Each alkyl halide solution (100 µL) was added to its corresponding well of a deep-well plate (1 x 88 x 1 format).

EXAMPLE 529:



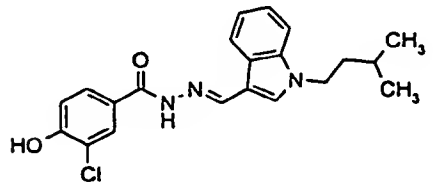
^{1}H NMR (DMSO-D_6): δ 1.14 (d, J = 6.8, 6H), 2.81 (sept, J = 6.9, 1H), 5.41 (s, 2H), 7.07 (d, J = 8.3, 1H), 7.20 (m, 6H), 7.54 (d, J = 7.6, 1H), 7.77 (d, J = 7.9, 1H), 7.97 (s, 1H), 8.01 (s, 1H), 8.29 (d, J = 7.2, 1H), 8.59 (s, 1H), 10.88 (s, 1H), 11.44 (s, 1H). LRMS calcd for C_{26} H_{24} Cl_1 N_3 O_2 (M - H) 445, found 445.9

EXAMPLE 530:

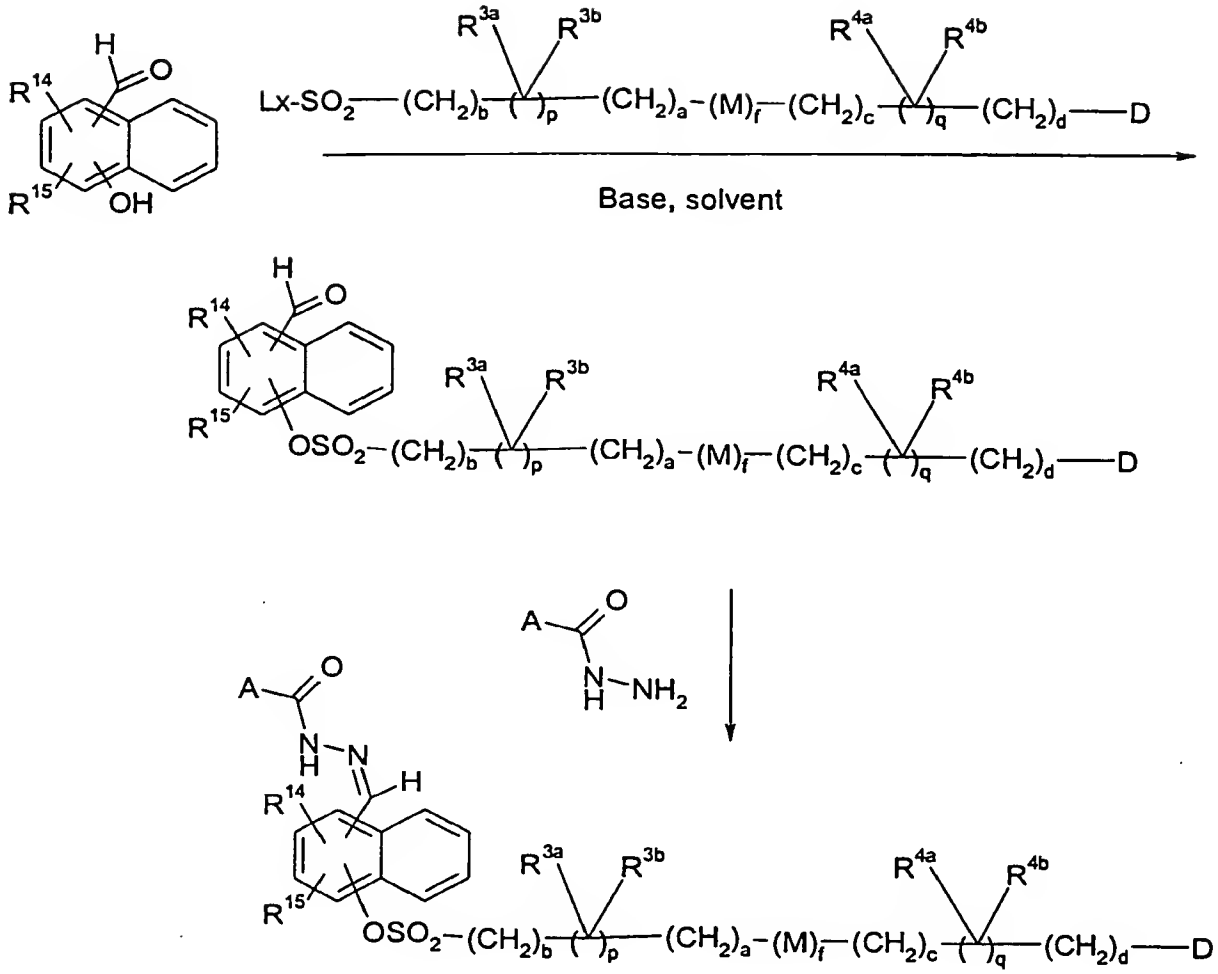


^{1}H NMR (DMSO-D_6): δ 5.47 (s, 2H), 7.08, (d, J = 8.7, 1H), 7.13-7.25 (m, 5H), 7.18 (t, J = 74.2, 1H), 7.35 (d, J = 8.7, 1H), 7.54 (d, J = 7.9, 1H), 7.77 (dd, J = 8.7, 1.7, 1H), 7.97 (d, J = 1.7, 1H), 8.02 (s, 1H), 8.30 (d, J = 7.2, 1H), 8.59 (s, 1H), 10.89 (s, 1H), 11.45 (s, 1H). LRMS calcd for C_{24} H_{18} Cl_1 F_2 N_3 O_3 (M - H) 468, found 468.1.

EXAMPLE 531:



^{1}H NMR (DMSO-D_6): δ 0.94 (d, J = 6.2, 6H), 1.54 (sept, J = 6.2, 1H), 1.66-1.73 (m, 2H), 4.23 (t, J = 7.0, 2H), 7.08 (d, J = 8.7, 1H), 7.16-7.29 (m, 2H), 7.54 (d, J = 7.95, 1H), 7.77 (d,



wherein Lx is a leaving group such as -Cl, -Br, -I, $-OSO_2CH_3$, $-OSO_2$p-tolyl or $-OSO_2CF_3$; and A, R^{3a}, R^{3b}, R^{4a}, R^{4b}, a, b, c, d, f, p, q, D, M, R^{14} and R^{15} are as defined for formula I.

According to the above scheme an alkyl/aryl-sulfonyloxyaryl aldehyde can be prepared by stirring hydroxybenzaldehydes or hydroxynaphthaldehydes in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, water or a compatible mixture of two or more of the above solvents with an equimolar amount of an alkylsulfonylhalide, arylsulfonylhalide or an aryl-lower alkyl sulfonylhalide and in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-

General procedures for the preparation of alkylidene hydrazides according to the invention involving parallel synthesis on a solid support:

The compounds of Examples 535 to 614 were prepared according to the following equation

Resin——[Building block 1] ⟶

Resin——[Building block 1]——[Building block 2] ⟶

Resin——[Building block 1]——[Building block 2]——[Building block 3]

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

[Building block 1]——[Building block 2]——[Building block 3].

The following 80 compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1]-[Building block 2] was done manually, whereas the attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

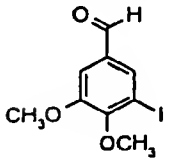
The starting resins, Resin-[Building block 1]-[Building block 2], were all prepared as described below.

The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

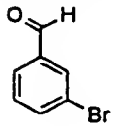
The following building blocks were used:

[Building block 2]:

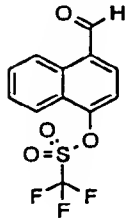
3,4-dimethoxy-5-iodobenzaldehyde



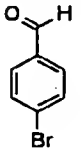
3-Bromobenzaldehyde



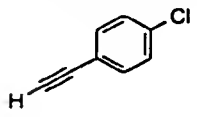
Trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester



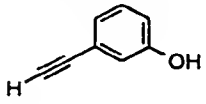
4-Bromobenzaldehyde



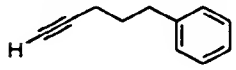
1-Chloro-4-ethynylbenzene



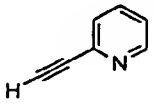
3-Ethynylphenol



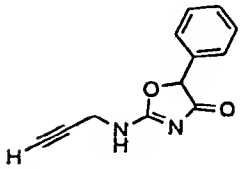
5-Phenyl-1-pentyne



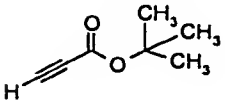
2-Ethynylpyridine



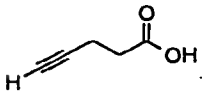
5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one



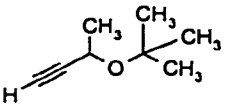
tert-Butyl propiolate



4-Pentynoic acid



tert-Butyl 1-methyl-2-propynyl ether



eluting with R_f = 0.46 were pooled and evaporated in vacuo to afford 8.35 g (47 %) of trifluoromethanesulfonic acid 4-formyl-1-naphthyl ester, m.p. 44-47 °C.
The other [Building block 2]'s (3-Bromobenzaldehyde and 4-bromobenzaldehyde) are commercially available.

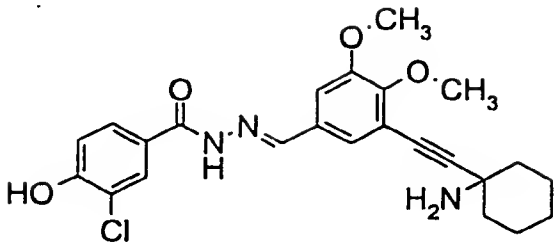
Preparation of Resin-[Building block 1]:
(Resin bound 3-chloro-4-hydroxybenzoic acid hydrazide)
Polystyrene resin (15 g) loaded with the Wang linker (0.92 mmoles/g), was successively washed with DMF (3 x 40 mL) and CH_2Cl_2 (3 x 40 mL). The resin was suspended in CH_2Cl_2 (80 mL) and diisopropylethylamine (60 mL) was added. The mixture was cooled to 0°C and methanesulfonyl chloride (5.8 mL) dissolved in CH_2Cl_2 (30 mL) was added drop wise while maintaining the temperature below 5 °C. When addition was complete the mixture was stirred at 0 °C for 30 minutes and at room temperature for 30 minutes. The resin was successively washed with CH_2Cl_2 (3 x 80 mL) and N-methylpyrrollidone (NMP) (3 x 80 mL). This resin and cesium carbonate (12.3 g) were added to ethyl 3-chloro-4-hydroxybenzoate (15 g) dissolved in NMP (200 mL) and the mixture was stirred at 80 °C for 4 hours. After cooling the resin was successively washed with NMP (3 x 80 mL) and methanol (3 x 80 mL).

The above resin was suspended in 1,4-dioxane (150 mL) and water (36 mL). Lithium hydroxide (2.6 g) was added and the mixture was stirred at 60 °C under N_2 for 16 hours. After cooling the resin was successively washed with DMF (3 x 80 mL), CH_2Cl_2 (3 x 80 mL) and methanol (80 mL) and dried in vacuo at 50 °C for 3 days.

The above resin (3.0 g) was suspended in CH_2Cl_2 (20 mL) and 1-hydroxybenzotriazole (0.6 g), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, hydrochloride (0.9 g) and DMF (10 mL) were added. The mixture was shaken at room temperature for 45 minutes, hydrazine hydrate (300 µL) was added, and the mixture was shaken overnight at room temperature. The resin was successively washed with DMF (3 x 20 mL) and CH_2Cl_2 (3 x 20 mL) to afford resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (Resin-[Building block 1]).

Preparation of Resin-[Building block 1]-[Building block 2]:
Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (3,4-dimethoxy-5-iodobenzylidene)hydrazide:

EXAMPLE 535:



3-Chloro-4-hydroxybenzoic acid [3-(1-aminocyclohexylethynyl)-4,5-dimethoxybenzylidene]-hydrazide

To the resin bound 3-chloro-4-hydroxybenzoic acid (3-bromobenzylidene)hydrazide (0.05 mmoles) was added copper (I) iodide (10 mg). Diisopropylethylamine (0.2 mL), a solution of triphenylphosphine in NMP (0.4 M, 0.5 mL), a solution of tetrabutylammonium chloride in water (0.66 M, 0.3 mL), a solution of palladium (II) acetate in NMP (0.16 M, 0.25 mL) and a solution of 1-ethynylcyclohexylamine ([Building block 3]) in NMP (1 M, 0.5 mL) were added successively, and the mixture was shaken at 90 °C for 15 hours. The resin was repeatedly washed with NMP (1.5 mL, 3 times), 50% water in DMF (1.5 mL, 3 times), NMP (1.5 mL, 2 times), 1% sodium diethylaminodithiocarbamate trihydrate (1.5 mL, 9 times), NMP (1.5 mL, 5 times), and CH_2Cl_2 (1.5 mL, 6 times) for 2 minutes and filtered.

The compound was cleaved off the resin by shaking for 45 minutes at room temperature with a 50% solution of trifluoroacetic acid in CH_2Cl_2 (1.5 mL). The mixture was filtered and the resin was extracted with CH_2Cl_2 (0.5 mL). The combined CH_2Cl_2 extracts were concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol and CH_2Cl_2 (1 mL) and concentrated in vacuo to give the title compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

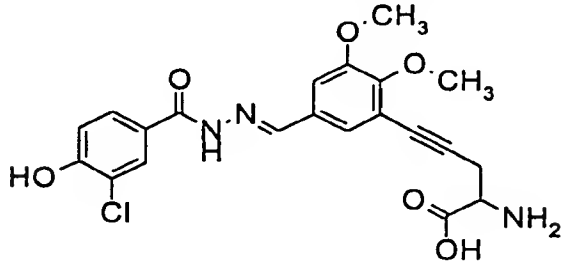
The RP-HPLC analysis was performed on a Waters HPLC system consisting of Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5 µ C-18 Symmetry column and Millenium

28 Transfer 1500µl from Reagent_3 [1] () to RB_Heating_All_1to96 [1-80] using NMP1
29 Mix for 3.00 minutes at 600 rpm(s)
30 Empty RB_Heating_All_1to96 for 2.000 minute(s)
31 Repeat from step 28, 2 times
32 Dispense System Fluid NMP1 1500µl to RB_Cleavage_All_1to96 [1-80]
33 Mix for 3.00 minutes at 600 rpm(s)
34 Empty RB_Heating_All_1to96 for 2.000 minute(s)
35 Repeat from step 32, 1 times
36 REM Wash with Sodium diethylaminodithiocarbamate
37 Transfer 1500µl from Reagent_3 [1] () to RB_Heating_All_1to96 [1-80] using NMP1
38 Mix for 3.00 minutes at 600 rpm(s)
39 Empty RB_Heating_All_1to96 for 2.000 minute(s)
40 Repeat from step 37, 2 times
41 Transfer 1500µl from REAGENT_4 [1] () to RB_Heating_All_1to96 [1-80] using NMP1
42 Mix for 3.00 minutes at 600 rpm(s)
43 Empty RB_Heating_All_1to96 for 2.000 minute(s)
44 Repeat from step 41, 2 times
45 Transfer 1500µl from REAGENT_5 [1] () to RB_Heating_All_1to96 [1-80] using NMP1
46 Mix for 2.00 minutes at 600 rpm(s)
47 Empty RB_Heating_All_1to96 for 2.000 minute(s)
48 Repeat from step 45, 2 times
49 Dispense System Fluid NMP1 1500µl to RB_Cleavage_All_1to96 [1-80]
50 Mix for 3.00 minutes at 600 rpm(s)
51 Empty RB_Heating_All_1to96 for 2.000 minute(s)
52 Repeat from step 49, 4 times
53 Dispense System Fluid DCE1 1500µl to RB_Cleavage_All_1to96 [1-80]
54 Mix for 3.00 minutes at 600 rpm(s)
55 Empty RB_Heating_All_1to96 for 2.000 minute(s)
56 Repeat from step 53, 5 times
57 REM Cleavage from Resin
58 REM with 50% TFA/DCM
59 Transfer 1500µl from Reagent _3 [1] () to RB_Cleavage_All_1to96 [1-80] using DCM1
60 Mix for 45.00 minutes at 600 rpm(s)
61 Empty RB_Cleavage_All_1to96 for 1.000 minute(s)
62 Dispense System Fluid DCM1 500µl to RB_Cleavage_All_1to96 [1-80]
63 Mix for 1.00 minutes at 300 rpm(s)
64 Empty RB_Cleavage_All_1to96 for 1.000 minute(s)
65
66

Dispense Sequence C:\ACT\ALKYNES.DSP is a subroutine that controls the combinatorial addition of the solutions of the 20 alkynes of type [Building block 3] into the 80 wells in the synthesizer.

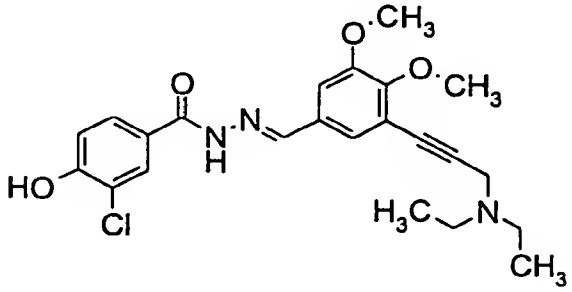
EXAMPLE 536:

2-Amino-5-{5-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentynoic acid



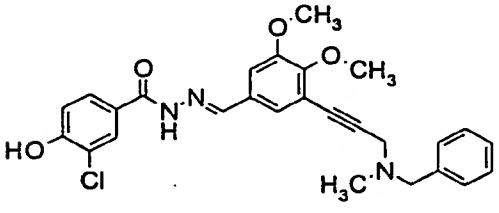
EXAMPLE 537:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propynyl)-4,5-dimethoxybenzylidene]hydrazide



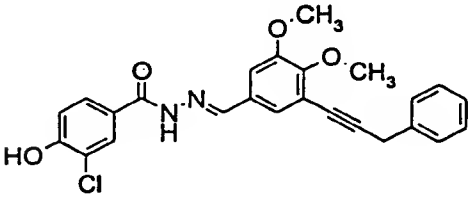
EXAMPLE 538:

3-Chloro-4-hydroxybenzoic acid{3-[3-(benzylmethylamino)-1-propynyl]-4,5-dimethoxybenzylidene}hydrazide



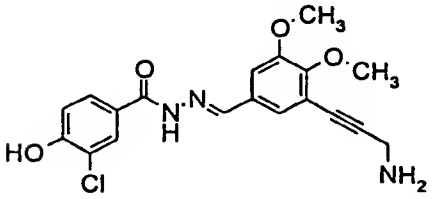
EXAMPLE 539:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenyl-1-propynyl)benzylidene]hydrazide



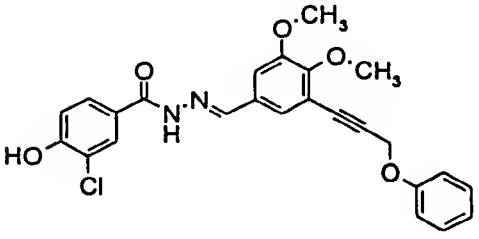
EXAMPLE 540:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propynyl)-4,5-dimethoxybenzylidene]hydrazide



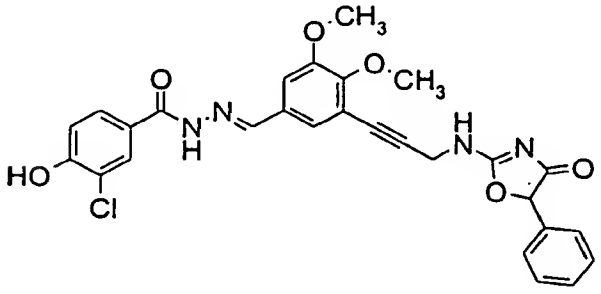
EXAMPLE 541:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenoxy-1-propynyl)benzylidene]hydrazide



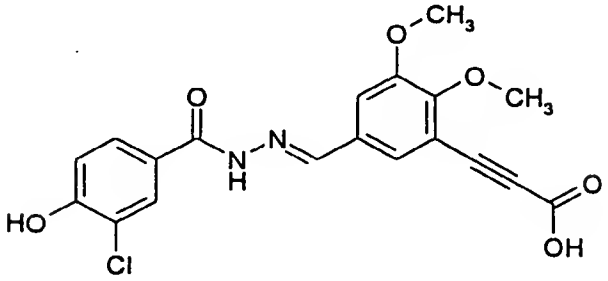
EXAMPLE 547:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[3-(4-oxo-5-phenyl-4,5-dihydro-2-oxazolylamino)-1-propynyl]-benzylidene}hydrazide



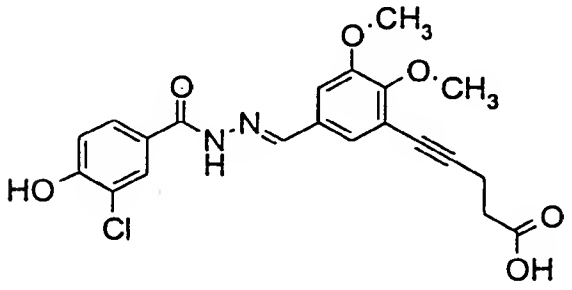
EXAMPLE 548:

{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxy-phenyl}propynoic acid



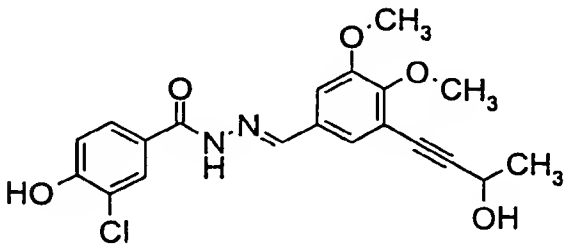
EXAMPLE 549:

5-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentynoic acid



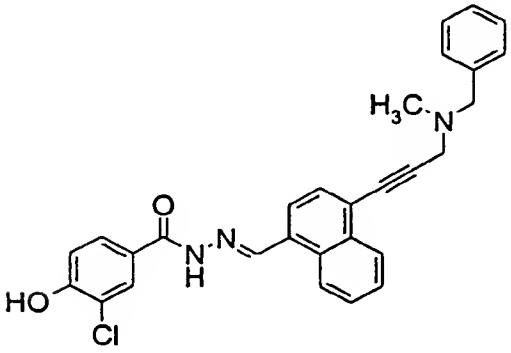
EXAMPLE 550:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butynyl)-4,5-dimethoxy-benzylidene]hydrazide



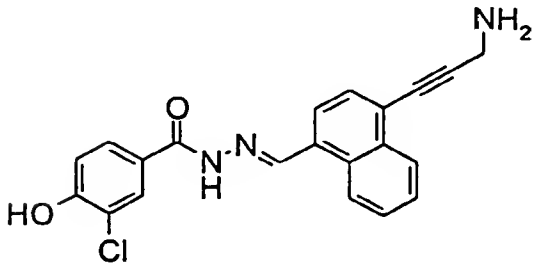
EXAMPLE 556:

3-Chloro-4-hydroxy benzoic acid [4-(3-benzylmethylamino-1-propynyl)-1-naphthylmethylene] hydrazide



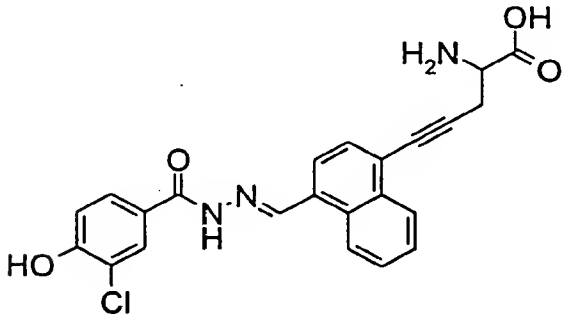
EXAMPLE 557:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propynyl)-1-naphthylmethylene]hydrazide



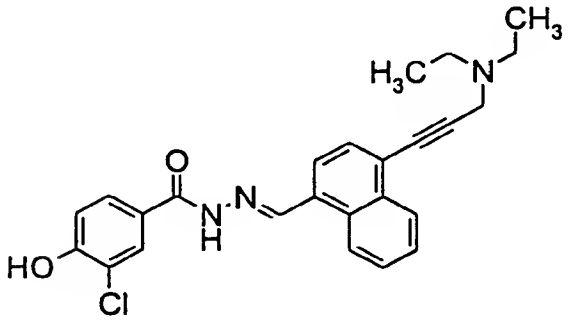
EXAMPLE 558:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentynoic acid



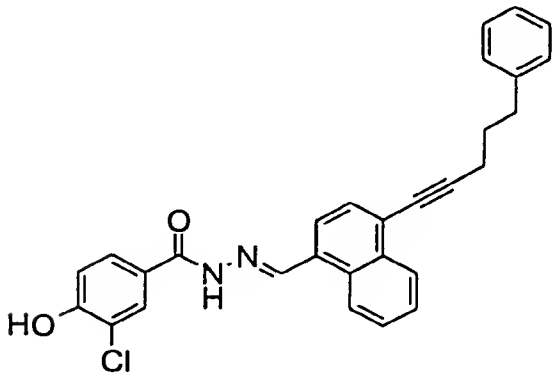
EXAMPLE 559:

3-Chloro-4-hydroxybenzoic acid[4-(3-diethylamino-1-propynyl)-1-naphthyl-methylene]hydrazide



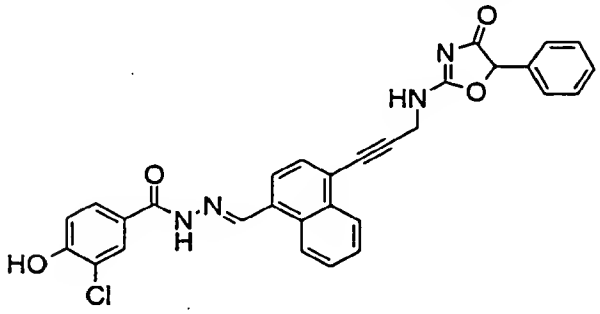
EXAMPLE 564:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentynyl)-1-naphthylmethylene]hydrazide



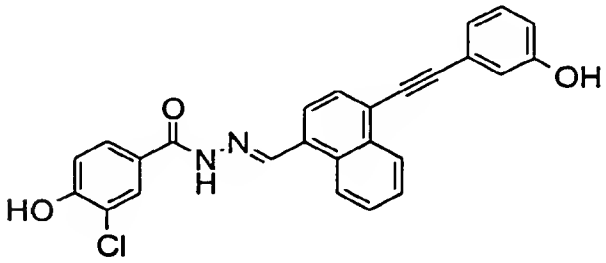
EXAMPLE 565:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propynyl]-1-naphthylmethylene}hydrazide



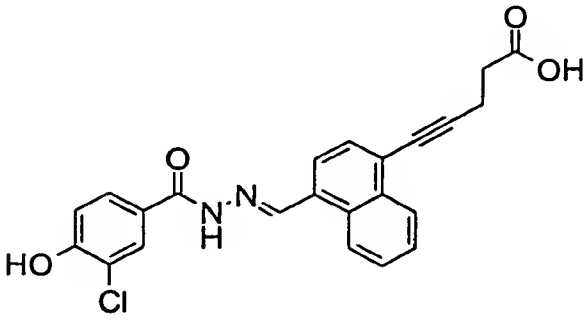
EXAMPLE 566:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxyphenylethynyl)-1-naphthyl-methylene]hydrazide



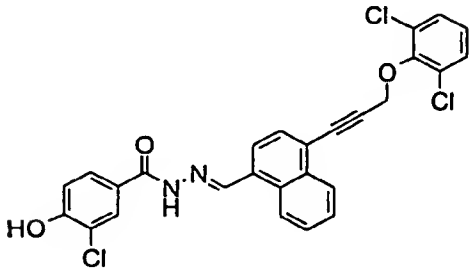
EXAMPLE 567:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentoic acid



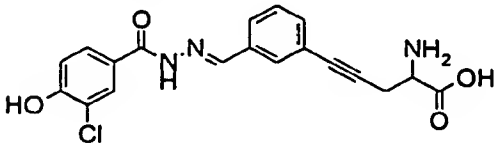
EXAMPLE 574:

3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-dichlorophenoxy)-1-propynyl]-1-naphthylmethylene}hydrazide



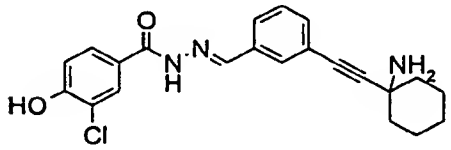
EXAMPLE 575:

2-Amino-5-{3-[(3-chloro-4-hydroxy-benzoyl)hydrazonomethyl]phenyl}-4-pentynoic acid



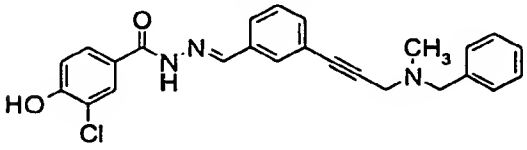
EXAMPLE 576:

3-Chloro-4-hydroxybenzoic acid [3-(1-aminocyclohexylethynyl)benzylidene]-hydrazide



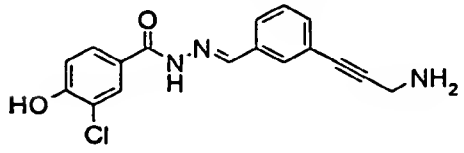
EXAMPLE 577:

3-Chloro-4-hydroxybenzoic acid {3-[3-(benzylmethylamino)-1-propynyl]benzylidene}hydrazide



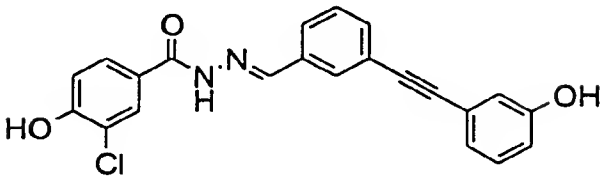
EXAMPLE 578:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propynyl)benzylidene]hydrazide



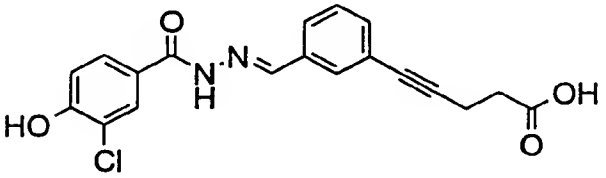
EXAMPLE 585:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxyphenylethynyl)benzylidene]-hydrazide



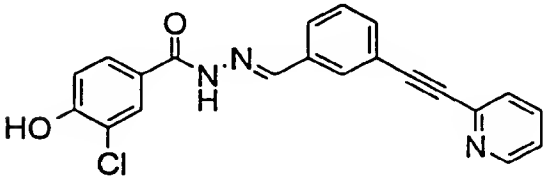
EXAMPLE 586:

5-{3-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentynoic acid



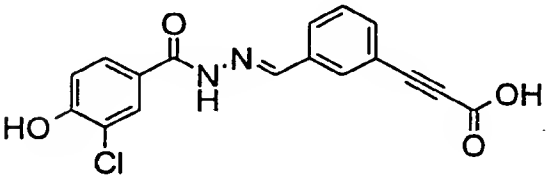
EXAMPLE 587:

3-Chloro-4-hydroxybenzoic acid [3-(2-pyridylethynyl)benzylidene]hydrazide



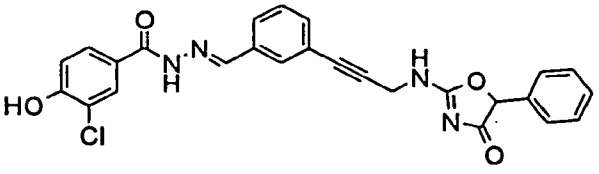
EXAMPLE 588:

{3-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}propynoic acid



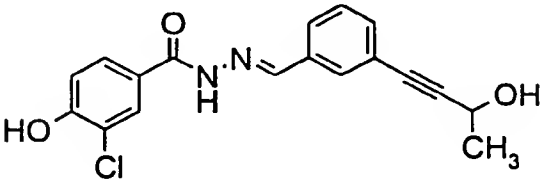
EXAMPLE 589:

3-Chloro-4-hydroxybenzoic acid {3-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino))-1-propynyl]benzylidene}hydrazide



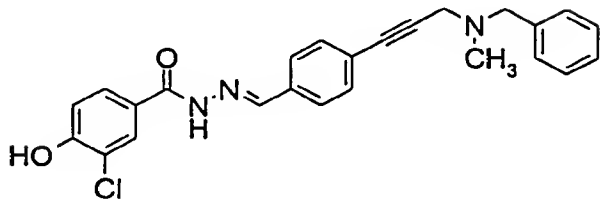
EXAMPLE 590:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butynyl)benzylidene]hydrazide



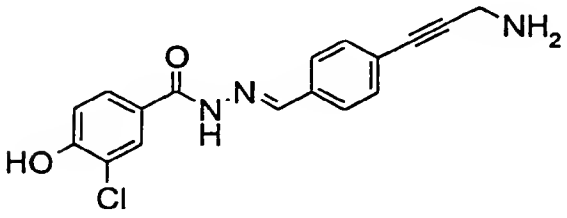
EXAMPLE 597:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)-1-propynyl]-benzylidene}hydrazide



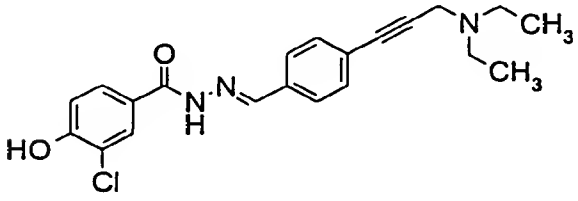
EXAMPLE 598:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propynyl)benzylidene]hydrazide



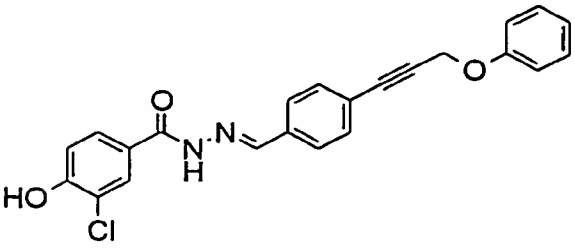
EXAMPLE 599:

3-Chloro-4-hydroxybenzoic acid [4-(3-diethylamino-1-propynyl)benzylidene]-hydrazide



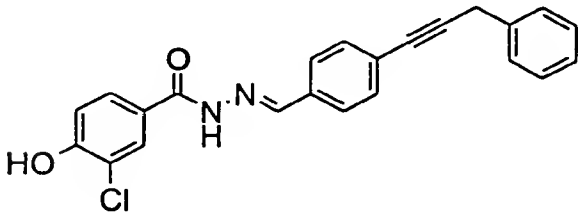
EXAMPLE 600:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propynyl]benzylidene]hydrazide



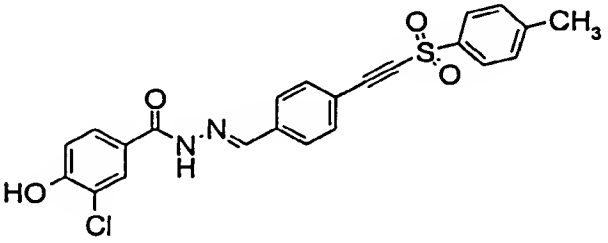
EXAMPLE 601:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenyl-1-propynyl)benzylidene]hydrazide



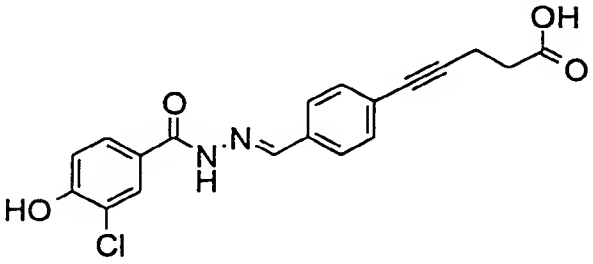
EXAMPLE 602:

3-Chloro-4-hydroxybenzoic acid [4-(toluene-4-sulfonylethynyl)benzylidene]hydrazide



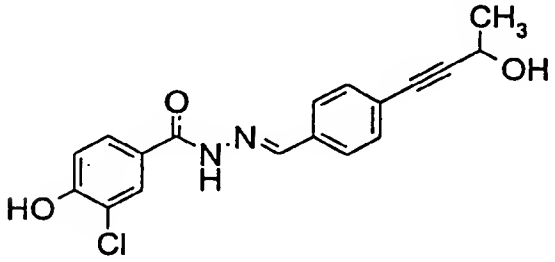
EXAMPLE 609:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentynoic acid



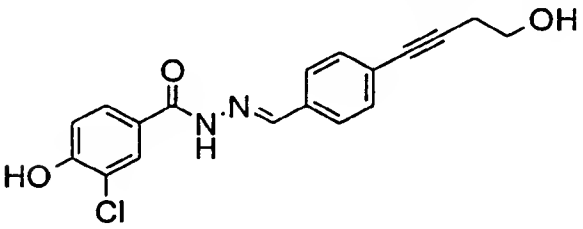
EXAMPLE 610:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-butynyl)benzylidene]hydrazide



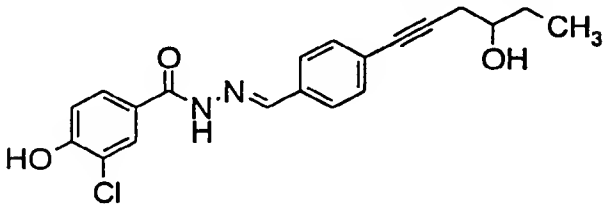
EXAMPLE 611:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-butynyl)benzylidene]hydrazide



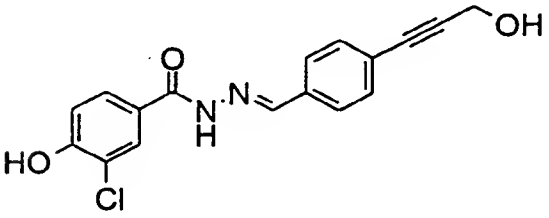
EXAMPLE 612:

-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexynyl)benzylidene]hydrazide



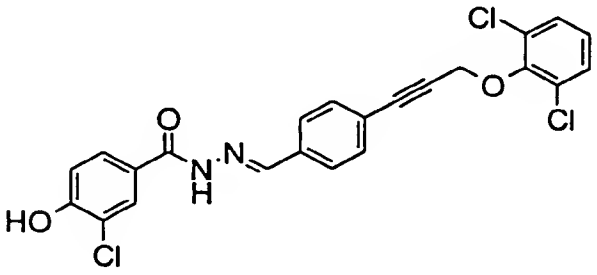
EXAMPLE 613:

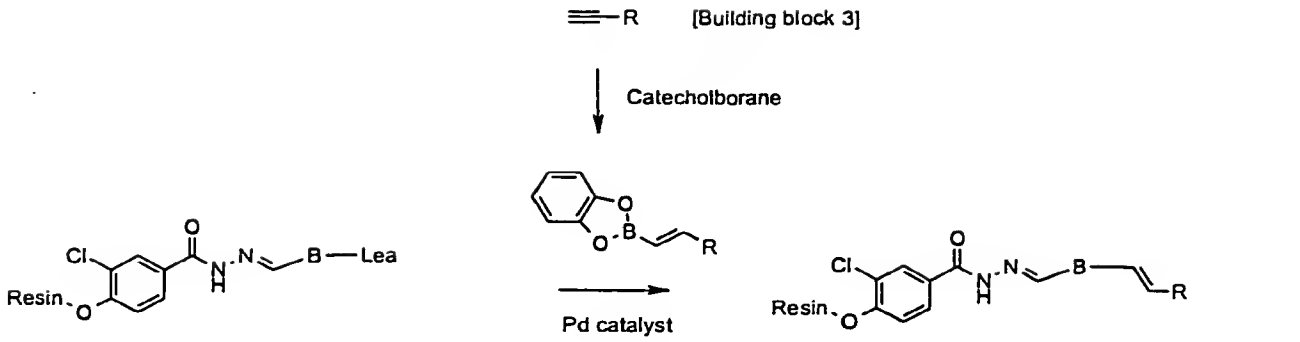
3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-propynyl)benzylidene]hydrazide



EXAMPLE 614:

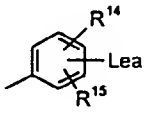
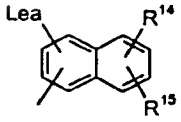
3-Chloro-4-hydroxybenzoic acid {4-[3-(2,6-dichlorophenoxy)-1-propynyl]benzylidene}-hydrazide





Resin-[Building block 1]-[Building block 2]

Resin-[Building block 1]-[Building block 2]-[Building block 3]

where B-Lea is  or 

wherein Lea is a leaving group and R^{14} and R^{15} are as defined for formula I.

The starting materials used were the same as those use in examples 535 to 614, i.e. Resin-[Building block 1], [Building block 2] and [Building block 3] were the same as those used in examples 535 to 614, the only difference being the products in examples 615 to 694 are having double bonds as compared to the products in examples 535 to 614 having triple bonds.

in vacuo. The residue was dissolved in a 1:1 mixture of methanol and CH_2Cl_2 (1 mL) and concentrated in vacuo to give the title compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

The RP-HPLC analysis was performed on a Waters HPLC system consisting of Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5 µ C-18 Symmetry column and Millenium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A gradient of 5% to 90% acetonitrile/0.1% trifluoroacetic acid/water at 15 minutes at 1 mL/minute.
The LC-MS analysis was performed on a PE Sciex API 100 LC/MS System using a Waters™ 3 mm x 150 mm 3.5 µ C-18 Symmetry column and positive ionspray with a flow rate at 20 µL/minute.

EXAMPLES 616 to 694:
A library of the following 79 compounds can be prepared in parallel as individual entities analogously to example 615 on an Advanced ChemTech Model 496 HTS using the following ChemFile to control the operation of the synthesizer. The 4 resins of type Resin-[Building block 1]-[Building block 2] are equally distributed in the 80 wells in the synthesizer prior to the initialization of device.

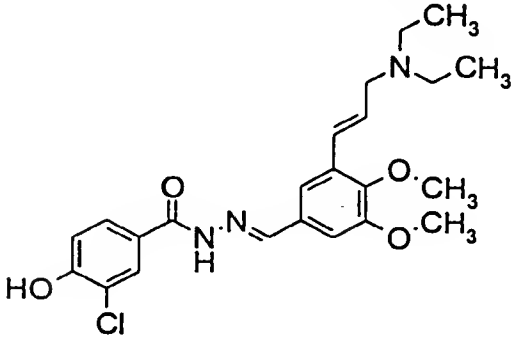
ChemFile C:\ACT\90250003.CHM Page 1
1 Empty RB_Heating_All_1to96 for 2.000 minute(s)
2
3 REM Addition of Cs2C03 in water
4
5 Transfer 200µl from Monomers_1to36 [25] () to RB_Heating_All_lto96 [1-80] using DCE
6 Mix for 1.00 minutes at 600 rpm(s)
7
8 REM Addition of Ph3P + Bu4NCl in NMP
9
10 Transfer 500µl from Monomers_1to36 [21] () to RB_Heating_All_1to96 [1-80] using DCE
11 Mix for 1.00 minutes at 600 rpm(s)
12
13 REM Addition of Pd(OAc)2 in NMP
14
15 Transfer 500µl from Monomers_1to36 [22] () to RB_Heating_All_1to96 [1-80] using DCE

```
65
66 REM Cleavage from Resin
67 REM with 50% TFA/DCM
68
69 Transfer 1500µl from Reagent_3 [1] () to RB_Cleavage_All_1to96 [1-80] using DCM1
70 Mix for 45.00 minutes at 600 rpm(s)
71 Empty RB_Cleavage_All_1to96 for 1.000 minute(s)
72 Dispense System Fluid DCM1 500µl to RB_Cleavage_All_1to96 [1-80]
73 Mix for 1.00 minutes at 300 rpm(s)
74 Empty RB_Cleavage_All_1to96 for 1.000 minute(s)
75
```

Dispense Sequence C:\ACT\ALKYNES.DSP is a subroutine that controls the combinatorial addition of the solutions of the 20 2-vinyl-benzo[1,3,2]dioxaboroles of type [Building block 3] into the 80 wells in the synthesizer.

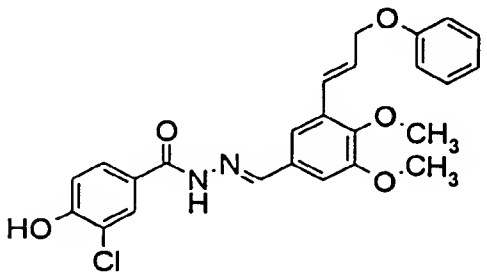
EXAMPLE 619:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propenyl)-4,5-dimethoxybenzylidene]hydrazide



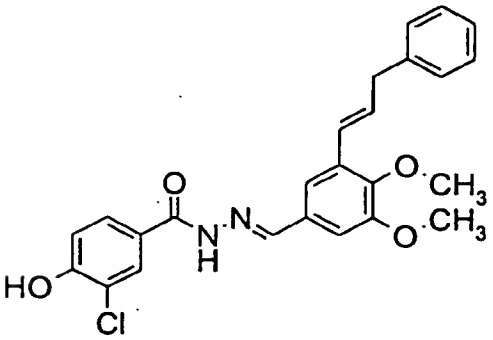
EXAMPLE 620:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenoxy-1-propenyl)-benzylidene]hydrazide



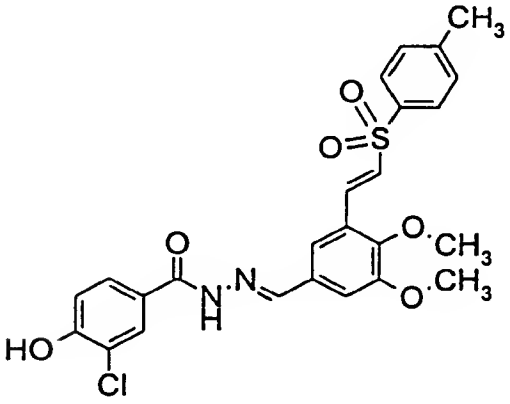
EXAMPLE 621:

3-Chloro-4-hydroxybenzoic acid [3,4-dimethoxy-5-(3-phenyl-1-propenyl)-benzylidene]hydrazide



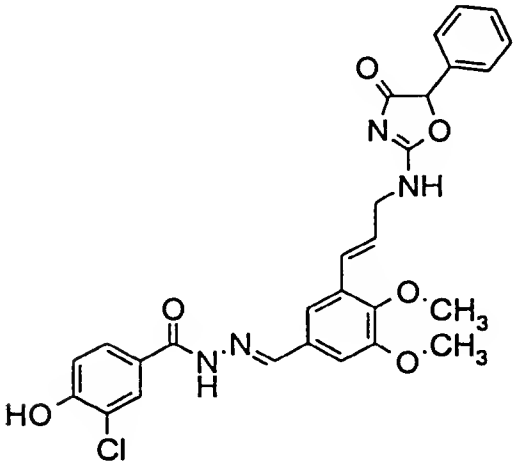
EXAMPLE 622:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[2-(toluene-4-sulfonyl)vinyl]-benzylidene}hydrazide



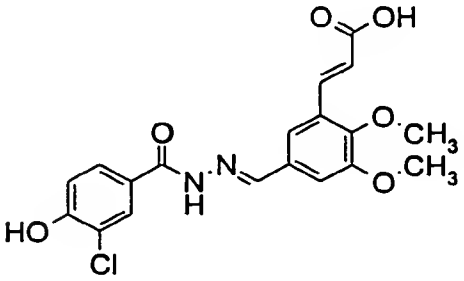
EXAMPLE 627:

3-Chloro-4-hydroxybenzoic acid {3,4-dimethoxy-5-[3-(4-oxo-5-phenyl-4,5-dihydro-2-oxazolylamino)-1-propenyl]-benzylidene}hydrazide



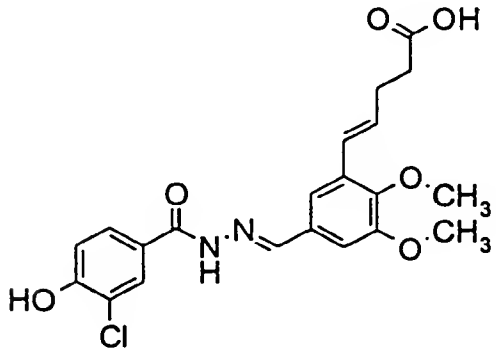
EXAMPLE 628:

3-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-acrylic acid



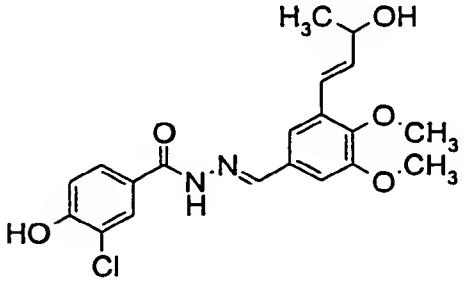
EXAMPLE 629:

5-{5-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-2,3-dimethoxyphenyl}-4-pentenoic acid



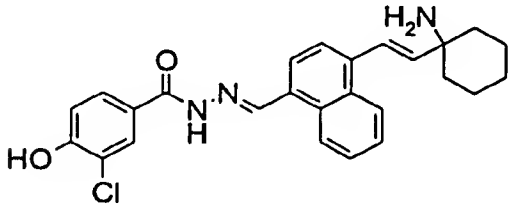
EXAMPLE 630:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-butenyl)-4,5-dimethoxy-benzylidene]hydrazide



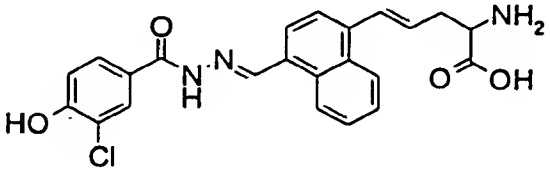
EXAMPLE 635:

3-chloro-4-hydroxybenzoic acid {4-[2-(1-aminocyclohexyl)vinyl]-1-naphthyl-methylene}hydrazide



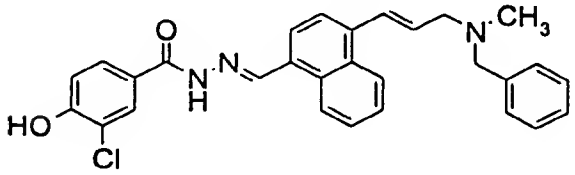
EXAMPLE 636:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentenoic acid



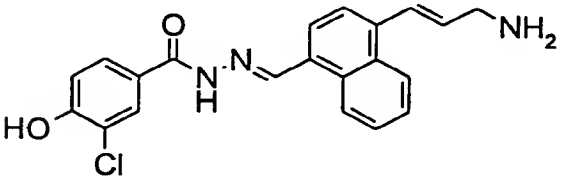
EXAMPLE 637:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)propenyl]-1-naphthylmethylene}hydrazide



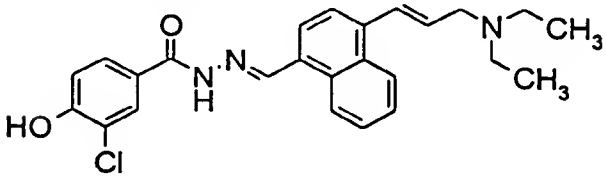
EXAMPLE 638:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propenyl)-1-naphthylmethylene]hydrazide



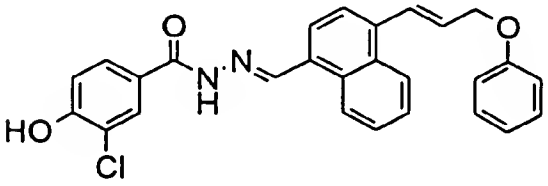
EXAMPLE 639:

3-Chloro-4-hydroxybenzoic acid[4-(3-diethylamino-1-propenyl)-1-naphthyl-methylene]hydrazide



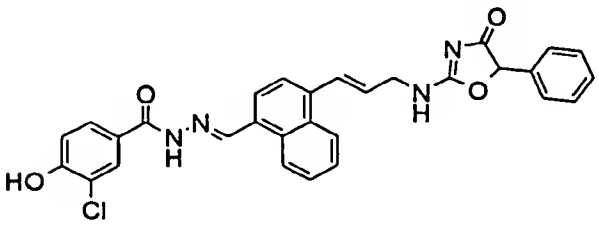
EXAMPLE 640:

3-Chloro-4-hydroxybenzoic acid [4-(3-phenoxy-1-propenyl)-1-naphthyl-methylene]hydrazide



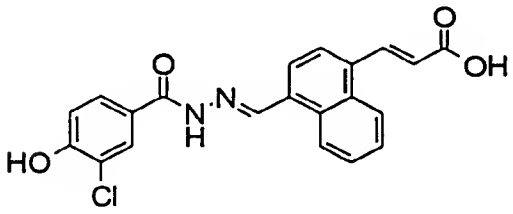
EXAMPLE 647:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propenyl]-1-naphthylmethylene}hydrazide



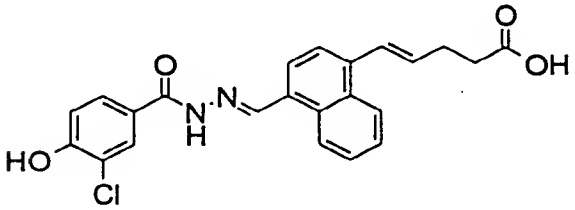
EXAMPLE 648:

3-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}acrylic acid



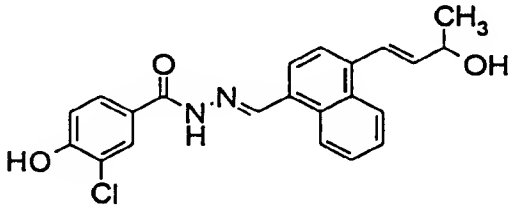
EXAMPLE 649:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthyl}-4-pentenoic acid



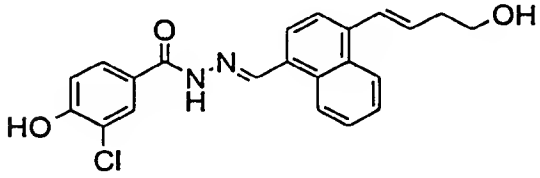
EXAMPLE 650:

3-Chloro-4-hydroxybenzoic acid [4-(3-hydroxy-1-butenyl)-1-naphthylmethylene]-hydrazide



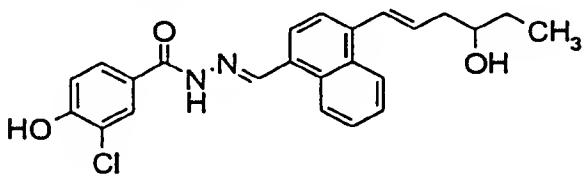
EXAMPLE 651:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-butenyl)-1-naphthylmethylene]-hydrazide



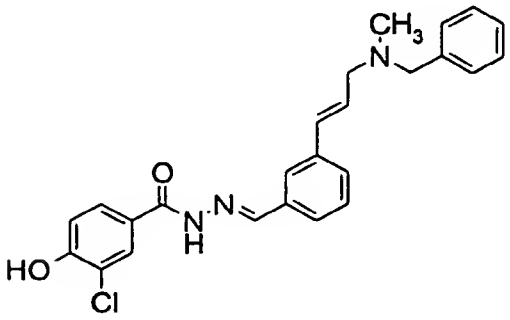
EXAMPLE 652:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexenyl)-1-naphthyl-methylene]hydrazide



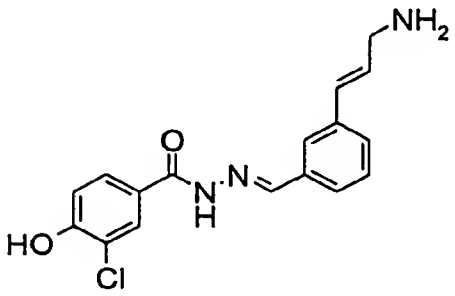
EXAMPLE 657:

3-Chloro-4-hydroxybenzoic acid {3-[3-(benzylmethylamino)-1-propenyl]-benzylidene}hydrazide



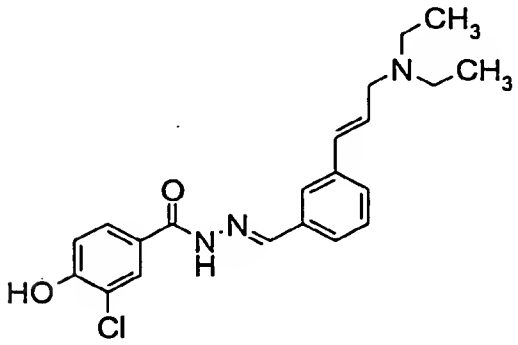
EXAMPLE 658:

3-Chloro-4-hydroxybenzoic acid [3-(3-amino-1-propenyl)benzylidene]hydrazide



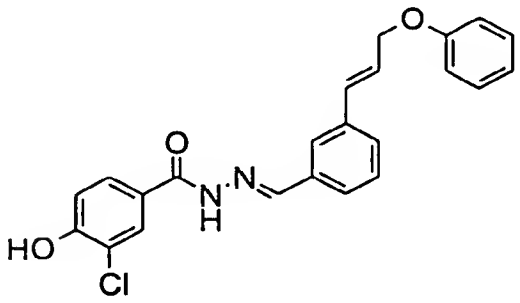
EXAMPLE 659:

3-Chloro-4-hydroxybenzoic acid [3-(3-diethylamino-1-propenyl)benzylidene]-hydrazide



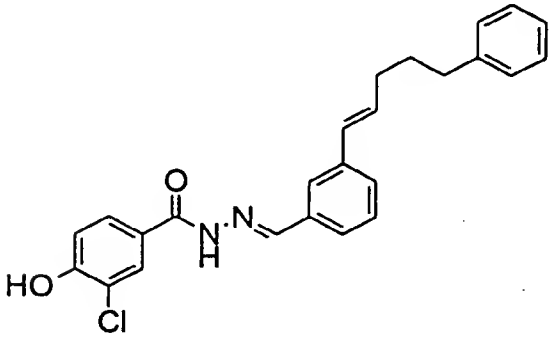
EXAMPLE 660:

3-Chloro-4-hydroxybenzoic acid [3-(3-phenoxy-1-propenyl)benzylidene]hydrazide



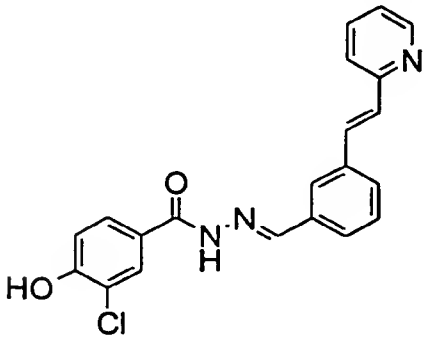
EXAMPLE 665:

3-Chloro-4-hydroxybenzoic acid [3-(5-phenyl-1-pentenyl)benzylidene]hydrazide



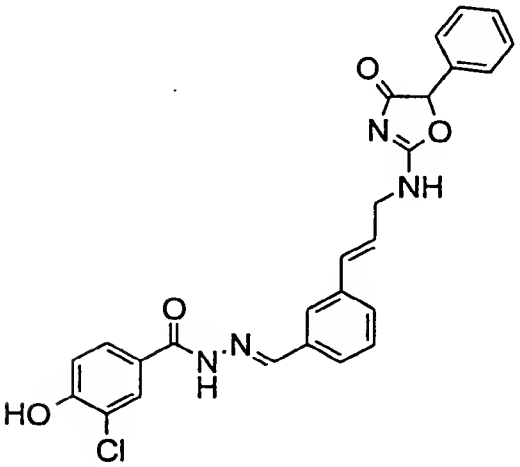
EXAMPLE 666:

3-Chloro-4-hydroxybenzoic acid [3-(2-(2-pyridyl)vinyl)benzylidene]hydrazide



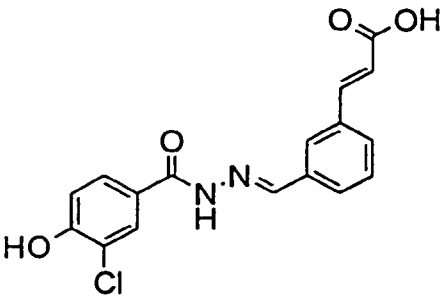
EXAMPLE 667:

3-Chloro-4-hydroxybenzoic acid {3-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino))-1-propenyl]benzylidene}hydrazide



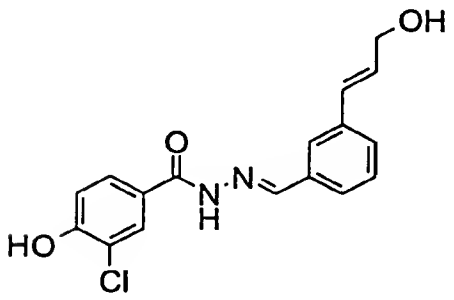
EXAMPLE 668:

3-{3-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}acrylic acid



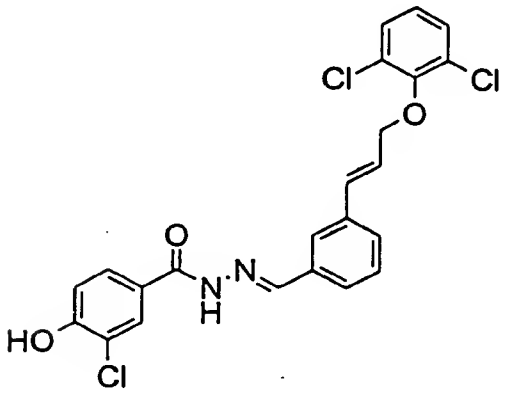
EXAMPLE 673:

3-Chloro-4-hydroxybenzoic acid [3-(3-hydroxy-1-propenyl)benzylidene]hydrazide



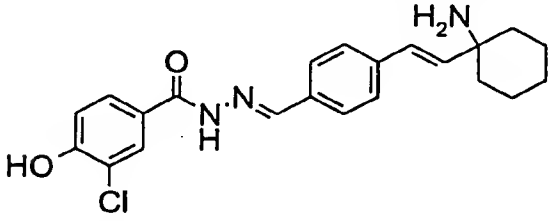
EXAMPLE 674:

3-Chloro-4-hydroxybenzoic acid {3-[3-(2,6-dichlorophenoxy)-1-propenyl]-benzylidene}hydrazide



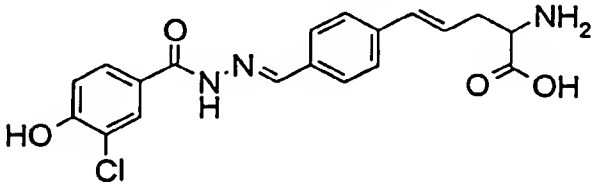
EXAMPLE 675:

3-Chloro-4-hydroxybenzoic acid {4-[2-(1-aminocyclohexyl)vinyl]benzylidene}hydrazide



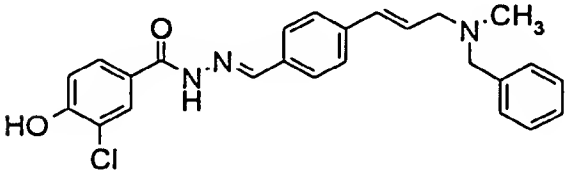
EXAMPLE 676:

2-Amino-5-{4-[(3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentenoic acid



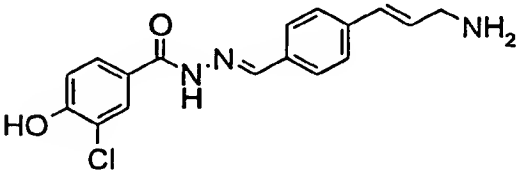
EXAMPLE 677:

3-Chloro-4-hydroxybenzoic acid {4-[3-(benzylmethylamino)-1-propenyl]-benzylidene}hydrazide



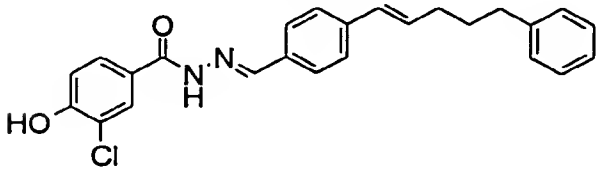
EXAMPLE 678:

3-Chloro-4-hydroxybenzoic acid [4-(3-amino-1-propenyl)benzylidene]hydrazide



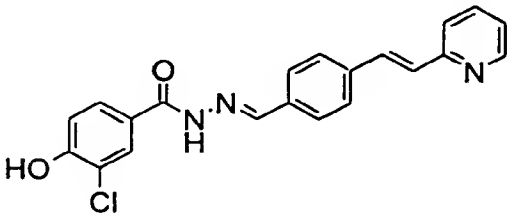
EXAMPLE 685:

3-Chloro-4-hydroxybenzoic acid [4-(5-phenyl-1-pentenyl)benzylidene]hydrazide



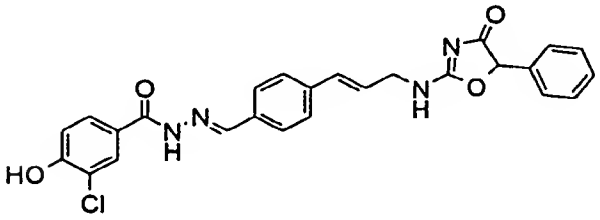
EXAMPLE 686:

3-Chloro-4-hydroxybenzoic acid {4-[2-(2-pyridinyl)vinyl]benzylidene}hydrazide



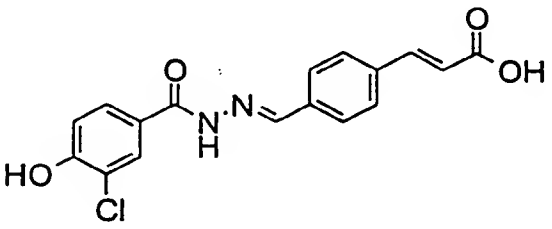
EXAMPLE 687:

3-Chloro-4-hydroxybenzoic acid {4-[3-(4-oxo-5-phenyl-4,5-dihydro-(2-oxazolylamino)-1-propenyl]benzylidene}hydrazide



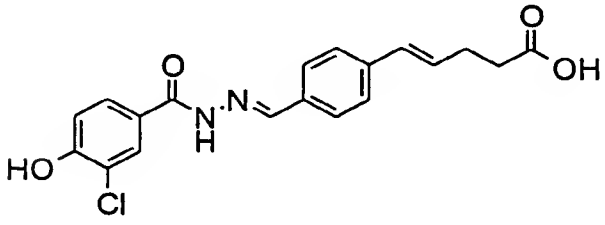
EXAMPLE 688:

{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}acrylic acid



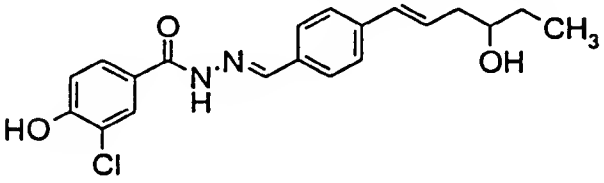
EXAMPLE 689:

5-{4-[(3-Chloro-4-hydroxybenzoyl)-hydrazonomethyl]phenyl}-4-pentenoic acid



EXAMPLE 690:

3-Chloro-4-hydroxybenzoic acid [4-(4-hydroxy-1-hexenyl)benzylidene]hydrazide



General Procedure for Examples 695 to 701:

The compounds were prepared as single entities according to the following equation

Resin——[Building block 1] ⟶

Resin——[Building block 1]——[Building block 2] ⟶

Resin——[Building block 1]——[Building block 2]——[Building block 3]

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

[Building block 1]——[Building block 2]——[Building block 3].

The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1] was done manually, whereas the attachment of [Building block 2] and [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 384 HTS.

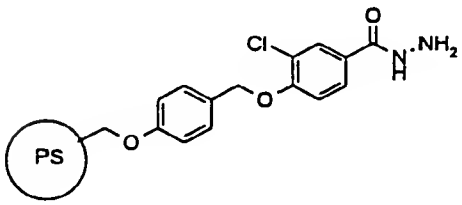
The starting resin, Resin-[Building block 1], was prepared as described above.

The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

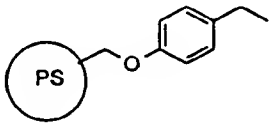
All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way using a nucleophilic substitution reaction according to the following formulae, which are included in the general formula II:

-D' where -D' is defined as a subset of -D that contains a primary or secondary amine that can react as a nucleophile.

The following resin, here depicted as Resin-[Building block 1] was used:

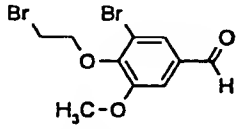
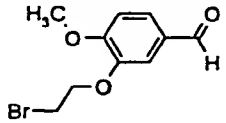
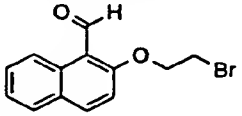
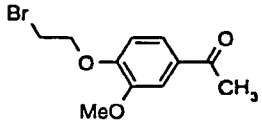


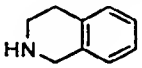
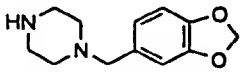
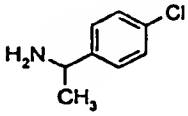
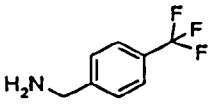
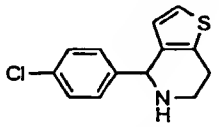
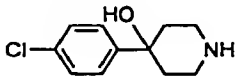
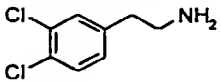
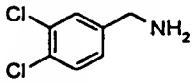
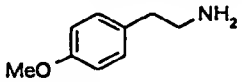
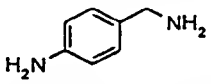
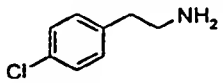
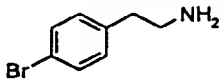
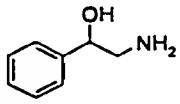
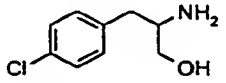
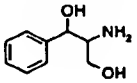
where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:



= Resin

The following building blocks were used:

4-(2-bromoethoxy)-3-bromo-5-methoxybenzaldehyde 	3-(2-bromoethoxy)-4-methoxybenzaldehyde 
2-(2-bromoethoxy)-1-naphthaldehyde 	4-(2-bromoethoxy)-3-methoxyacetophenone 

1,2,3,4-tetrahydroisoquinoline 	1-(3,4-methylenedioxybenzyl)-piperazine 	4-chloro-α-methylbenzylamine 
4-(trifluoromethyl)-benzylamine 	4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine 	4-(4-chlorophenyl)-4-hydroxypiperidine 
3,4-dichlorophenethylamine 	3,4-dichlorobenzylamine 	4-methoxyphenethylamine 
4-aminobenzylamine 	4-chlorophenethylamine 	4-bromophenethylamine 
2-amino-1-phenylethanol 	2-amino-3-(4-chlorophenyl)-1-propanol 	2-amino-1-phenyl-1,3-propanediol 

DMF (130 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.8 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (400 mL), dried over $MgSO_4$ and evaporated in vacuo to afford 17.4 g (99%) of 4-(2-bromoethoxy)-2-methoxybenzaldehyde, M.p. 78 - 79 °C.

Preparation of 4-(2-bromoethoxy)-3-methoxybenzaldehyde:

1,2-Dibromoethane (57 mL, 0.66 moles) was added to a mixture of 4-hydroxy-3-methoxybenzaldehyde (10 g, 66 mmoles) and potassium carbonate (45 g, 0.33 moles) in DMF (130 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (1.2 L) and extracted with ethyl acetate (500 + 4 x 300 mL). The combined organic phases were washed with saturated sodium chloride (500 mL), dried over $MgSO_4$ and evaporated in vacuo to afford 16.3 g (95%) of 4-(2-bromoethoxy)-3-methoxybenzaldehyde. M.p. 61 - 64 °C.

Preparation of 4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde:

1,2-Dibromoethane (46 mL, 0.54 moles) was added to a mixture of 3-chloro-4-hydroxy-5-methoxybenzaldehyde (10 g, 54 mmoles) and potassium carbonate (37 g, 0.27 moles) in DMF (180 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with saturated sodium chloride (150 mL), dried over $MgSO_4$ and evaporated in vacuo to afford 9.33 g (59%) of 4-(2-bromoethoxy)-3-chloro-5-methoxybenzaldehyde. M.p. 52 - 54 °C.

Preparation of 4-(2-bromoethoxy)-3,5-dimethylbenzaldehyde:

1,2-Dibromoethane (26 mL, 0.3 moles) was added to a mixture of 3,5-dimethyl-4-hydroxybenzaldehyde (4.57 g, 30 mmoles) and potassium carbonate (21 g, 150 mmoles) in DMF (90 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.3 L), added saturated sodium chloride (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed

heated at reflux under N_2 for 16 hours. After cooling the mixture was diluted with water (150 mL) and washed with heptane (400 mL) . The aqueous phase was made acidic with 3N hydrochloric acid and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography over silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:2) to afford 5.49 g (77%) of 4-hydroxy-3-methoxy-5-phenylbenzaldehyde. M.p. 107 - 108 °C.

1,2-Dibromoethane (41 mL, 0.48 moles) was added to a mixture of the above 4-hydroxy-3-methoxy-5-phenylbenzaldehyde (5.49 g, 24 mmoles) and potassium carbonate (17 g, 123 mmoles) in DMF (80 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (200 mL), dried over $MgSO_4$ and evaporated in vacuo to afford 8.1 g (100%) of 4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde as an oil.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.50 (2H, t), 3.96 (3H, s), 4.19 (2H, t), 7.4-7.6 (11H, m).

Preparation of 4-(2-bromoethoxy)-1-naphthaldehyde:

1,2-Dibromoethane (30 mL, 0.35 moles) was added to a mixture of 4-hydroxy-1-naphthaldehyde (6 g, 35 mmoles) and potassium carbonate (24 g, 175 mmoles) in DMF (110 ml) and the resulting mixture was stirred vigorously at room temperature for 16 hours. The mixture was poured into water (0.5 L) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were washed with saturated sodium chloride (300 mL), dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (800 mL) eluting with a mixture of ethyl acetate and heptane (1:1) to afford 8.5 g (88%) of 4-(2-bromoethoxy)-1-naphthaldehyde as a solid. M.p.: 83 - 84 °C.

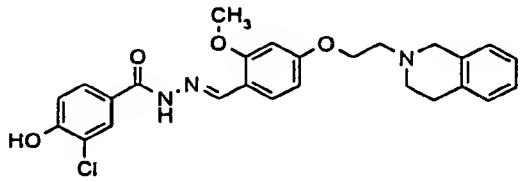
Calculated for $C_{13}H_{11}BrO_2$: C, 55.94%; H, 3.97%.
Found: C, 56.10%; H, 3.98%; C, 56.30%; H, 3.97%.

Preparation of 4-(2-bromoethoxy)-3,5-dimethoxybenzaldehyde:

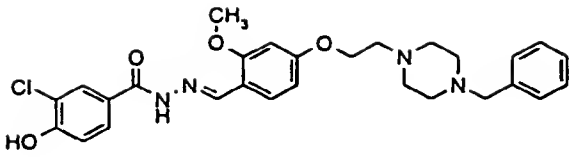
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.79 (2H, t), 3.93 (3H, s), 4.40 (2H, t), 7.55 (1H, d), 7.79 (1H, d).

EXAMPLE 695:

Preparation of 3-Chloro-4-hydroxybenzoic acid {4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzylidene}hydrazide



The resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block1]) (3 g, ~3 mmoles) was swelled in DMF (35 mL) for 30 minutes. Then 4-(2-bromoethoxy)-2-methoxybenzaldehyde (2.33 g, 9 mmoles) and triethyl orthoformate (18 mL) were added and the mixture was shaken at room temperature for 16 hours. The resin was repeatedly swelled in DMF (35 ml, 4 times), CH_2Cl_2 (35 mL, 6 times) and N-methyl-2-pyrrolidinone (NMP) (35 mL, 2 times) and filtered. The resin was swelled in NMP (40 mL) and 1,2,3,4-tetrahydroisoquinoline (3.75 mL, 30 mmoles) and potassium iodide (1.0 g, 6 mmoles) were added. The resin was shaken at room temperature for 16 hours and filtered. The resin was repeatedly swelled in DMF (40 ml, 5 times), CH_2Cl_2 (40 mL, 10 times) and filtered. The compound was cleaved off the resin by shaking for 1 hour at room temperature with a 50% solution of trifluoroacetic acid in CH_2Cl_2 (40 mL). The mixture was filtered and the resin was extracted with CH_2Cl_2 (40 mL, 2 times). The combined CH_2Cl_2 extracts were concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (40 mL) and concentrated in vacuo. The residue was dissolved in methanol (40 mL) and concentrated in vacuo. The residue was partitioned between ethyl acetate (50 mL) and saturated sodium hydrogencarbonate (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by coloumn chromatography over silica gel (200 mL) eluting with a mixture of CH_2Cl_2 and methanol (9:1). This afforded 280 mg of the title compound.



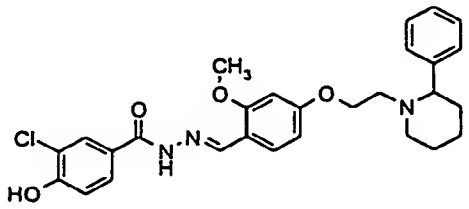
This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-2-methoxybenzaldehyde ([building block 2]) (0.73 g, 1.5 equivs.), and 1-benzylpiperazine ([building block 3]) (3.3 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue (1.4 g) was dissolved in 2-propanol (50 ml) and concentrated to 20 ml. The mixture was allowed to stand at 5 °C for 1 h and filtered. The mother liquor was concentrated in vacuo and the residue was purified by column chromatography on silica gel (20 g) eluting with a mixture of methanol and dichloromethane (1:9). This afforded 0.98 g of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ_H = 2.4 (2H, bs), 2.55 (2H, bs), 2.62 (2H, bs), 3.50 (2H, bs), 3.85 (3H, s), 4.15 (2H, t), 6.62 (2H, m), 7.05 (1H, d), 7.30 (5H, m), 7.75 (2H, t), 7.97 (1H, s), 8.67 (1H, s), 11 (1H, bs), 11.5 (1H, s).

HPLC-MS (METHOD A): R_t = 7.7 min; m/z = 523 (M+1).

EXAMPLE 698:

3-Chloro-4-hydroxybenzoic acid {2-methoxy-4-[2-(2-phenylpiperidin-1-yl)ethoxy]benzylidene}hydrazide



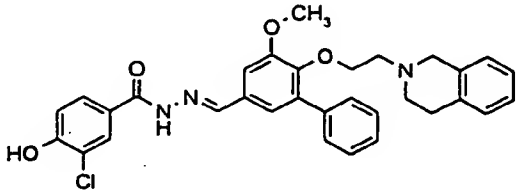
This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-2-methoxybenzaldehyde ([building block 2])

^{1}H-NMR (400 MHz, DMSO-d_6): δ_H = 1.9 (1H, p), 2.18 (1H, t), 2.90 (2H, t), 3.70 (2H, s), 3.90 (3H, s), 4.19 (2H, t), 7.05 (5H, m), 7.37 (2H, s), 7.78 (1H, d), 7.95 (1H, s), 8.33 (1H, s), 11 (1H, bs), 11.8 (1H, s).

HPLC-MS (METHOD A): R_t = 9.0 min; m/z = 514 (M+1).

EXAMPLE 700:

3-Chloro-4-hydroxybenzoic acid {6-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)ethoxy]-5-methoxybiphenyl-3-ylmethylene}hydrazide



This compound was prepared analogously to the compound described in the previous example starting from resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) (2 g, ~2 mmoles), 4-(2-bromoethoxy)-3-methoxy-5-phenylbenzaldehyde ([building block 2]) (0.93 g, 1.5 equivs.), and 1,2,3,4-tetrahydroisoquinoline ([building block 3]) (2.5 g, 10 equivs.). After cleavage with 50% trifluoroacetic acid, the residue was dissolved in 15 ml of a mixture of 25% aq. ammonia, methanol and dichloromethane (1:9:90) and purified by column chromatography on silica gel (25 g) eluting with a mixture of methanol and dichloromethane (1:12). This afforded 0.31 g of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ_H = 2.60 (4H, m), 2.70 (2H, m), 3.48 (2H, s), 3.92 (3H, s), 3.96 (2H, t), 6.98 (1H, m), 7.10 (4H, m), 7.22 (1H, s), 7.40 (4H, m), 7.55 (2H, d), 7.78 (1H, d), 8.00 (1H, s), 8.40 (1H, s), 11 (1H, bs), 11.7 (1H, s).

HPLC-MS (METHOD A): R_t = 9.6 min; m/z = 557 (M+1).

EXAMPLE 701:

Further, a library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2] and [building block 3]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

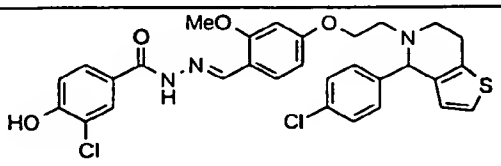
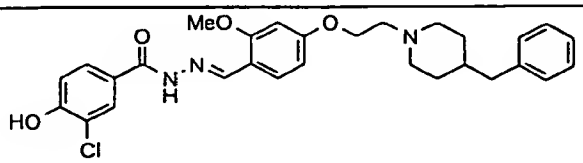
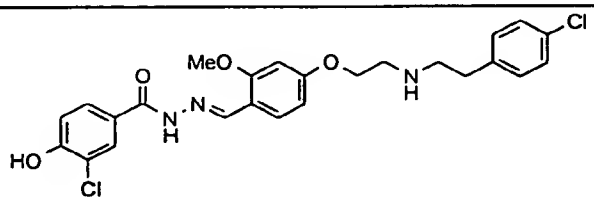
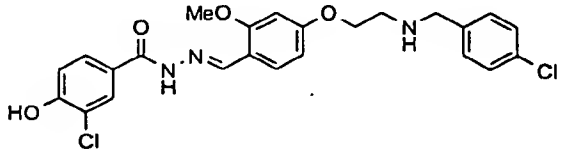
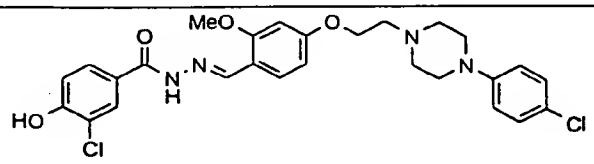
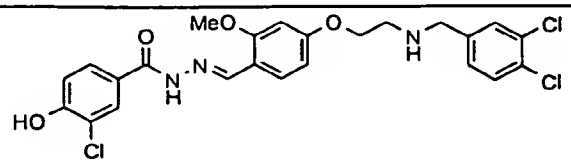
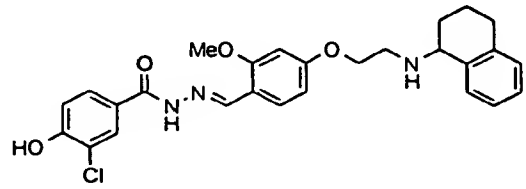
The resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) is equally distributed in the wells in the synthesizer prior to the initialization of the device.

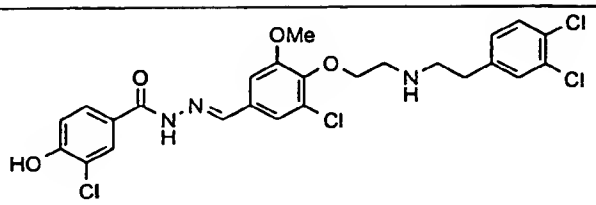
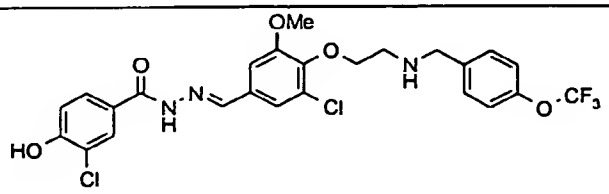
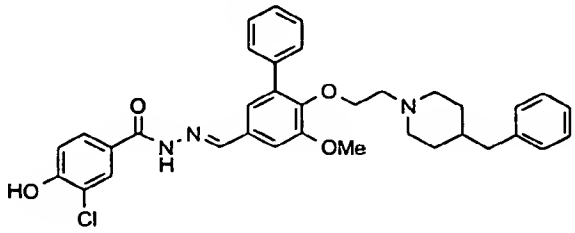
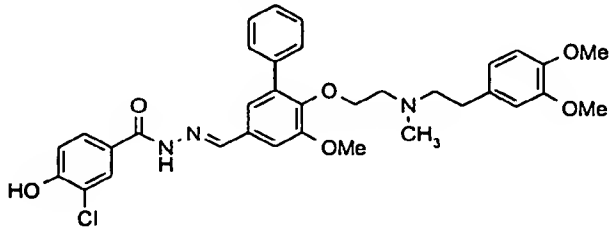
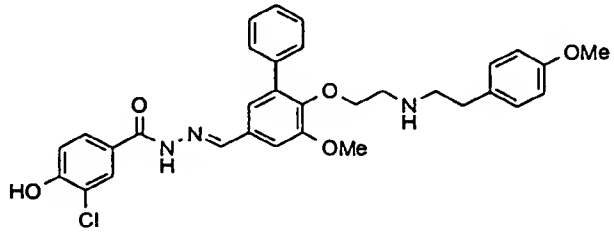
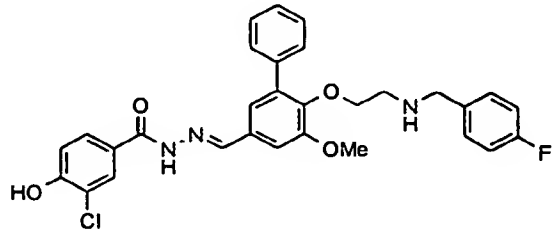
ChemFile C:\ACT_1328\90250012.CHM:

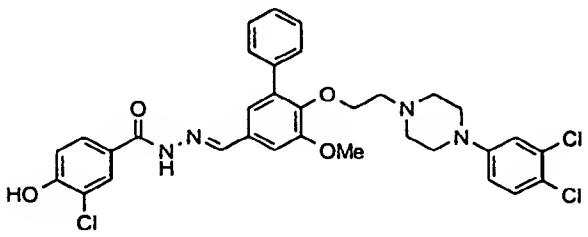
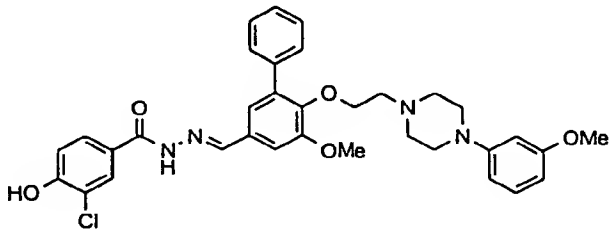
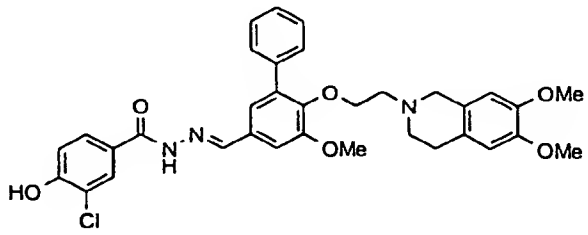
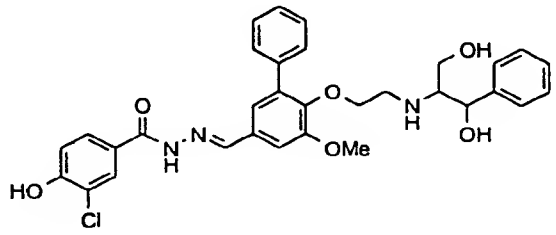
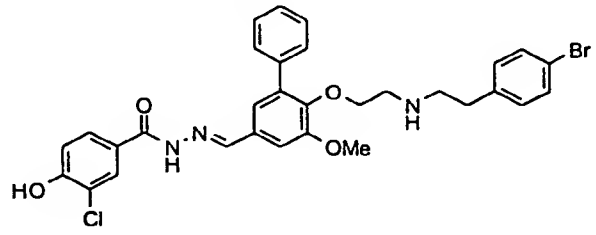
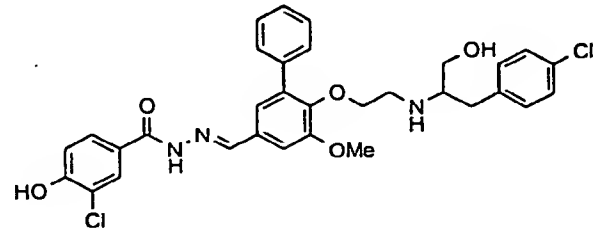
```
1 REM Filtration of resin
2 Empty RB1_1to96 for 5.000 minute(s)
3 Empty RB2_1to96 for 5.000 minute(s)
4 Empty RB3_1to96 for 5.000 minute(s)
5 Empty RB4_1to96 for 5.000 minute(s)
6 Pause
7
8 REM Washing of resin
9
10 Dispense System Fluid Disdu1_4* 1500ul to RB1_1to96[1-96]
11 Dispense System Fluid Disdu1_4* 1500ul to RB2_1to96[1-96]
12 Dispense System Fluid Disdu1_4* 1500ul to RB3_1to96[1-96]
13 Dispense System Fluid Disdu1_4* 1500ul to RB4_1to96[1-96]
14 Start mixing "RB1_1to96" for 5.00 minutes at 600 rpm(s) and continue.
15 Start mixing "RB2_1to96" for 5.00 minutes at 600 rpm(s) and continue.
16 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s) and continue.
17 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
18 Wait for 25.000 minute(s)
19 Repeat from step 14, 1000 times
20 Empty RB1_1to96 for 5.000 minute(s)
21 Empty RB2_1to96 for 5.000 minute(s)
22 Empty RB3_1to96 for 5.000 minute(s)
23 Empty RB4_1to96 for 5.000 minute(s)
24 Pause
25
26 REM Coupling with aldehydes
27
28 Dispense System Fluid Disdu2_3* 1500ul to RB1_1to96[1-96]
29 Dispense System Fluid Disdu2_3* 1500ul to RB2_1to96[1-96]
30 Dispense System Fluid Disdu2_3* 1500ul to RB3_1to96[1-96]
31 Dispense System Fluid Disdu2_3* 1500ul to RB4_1to96[1-96]
```

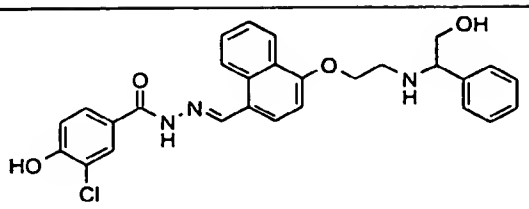
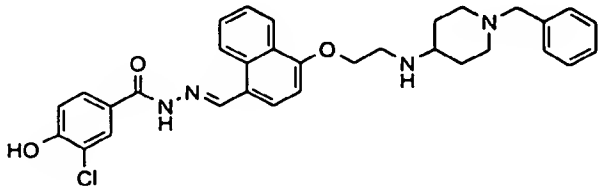
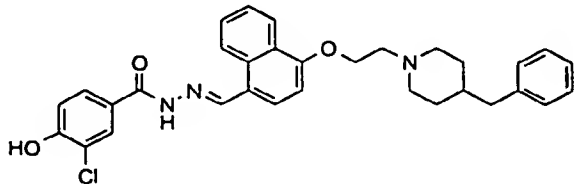
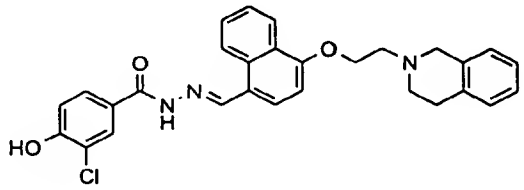
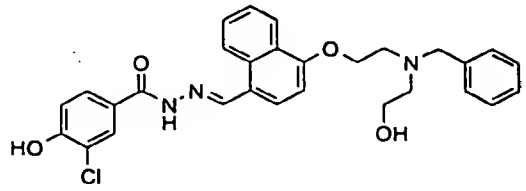
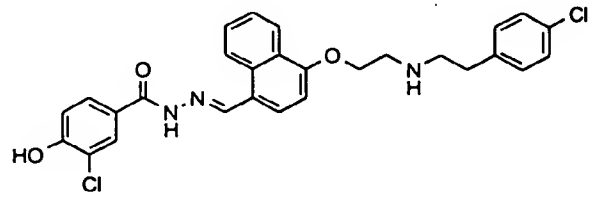
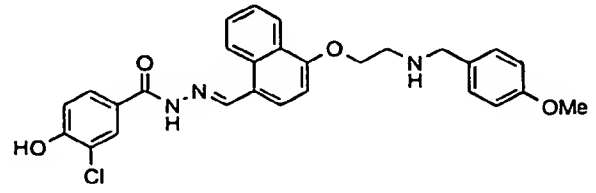
81 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
82 Empty RB1_1to96 for 5.000 minute(s)
83 Empty RB2_1to96 for 5.000 minute(s)
84 Empty RB3_1to96 for 5.000 minute(s)
85 Empty RB4_1to96 for 5.000 minute(s)
86 Repeat from step 74, 2 times
87 Pause
88 Dispense System Fluid Disdu1_4* 1500ul to RB1_1to96[1-96]
89 Dispense System Fluid Disdu1_4* 1500ul to RB2_1to96[1-96]
90 Dispense System Fluid Disdu1_4* 1500ul to RB3_1to96[1-96]
91 Dispense System Fluid Disdu1_4* 1500ul to RB4_1to96[1-96]
92 Start mixing "RB1_1to96" for 5.00 minutes at 600 rpm(s) and continue.
93 Start mixing "RB2_1to96" for 5.00 minutes at 600 rpm(s) and continue.
94 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s) and continue.
95 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
96 Empty RB1_1to96 for 5.000 minute(s)
97 Empty RB2_1to96 for 5.000 minute(s)
98 Empty RB3_1to96 for 5.000 minute(s)
99 Empty RB4_1to96 for 5.000 minute(s)
100 Repeat from step 88, 1 times
101 Dispense System Fluid Disdu2_3* 1500ul to RB1_1to96[1-96]
102 Dispense System Fluid Disdu2_3* 1500ul to RB2_1to96[1-96]
103 Dispense System Fluid Disdu2_3* 1500ul to RB3_1to96[1-96]
104 Dispense System Fluid Disdu2_3* 1500ul to RB4_1to96[1-96]
105 Start mixing "RB1_1to96" for 5.00 minutes at 600 rpm(s) and continue.
106 Start mixing "RB2_1to96" for 5.00 minutes at 600 rpm(s) and continue.
107 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s) and continue.
108 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
109 Wait for 25.000 minute(s)
110 Repeat from step 105, 1000 times
111 Pause
112 Empty RB1_1to96 for 5.000 minute(s)
113 Empty RB2_1to96 for 5.000 minute(s)
114 Empty RB3_1to96 for 5.000 minute(s)
115 Empty RB4_1to96 for 5.000 minute(s)
116 Repeat from step 101, 1 times
117
118 REM Coupling with amines
119 Flush Arm1 with Disdu2_3*, Arm2 with Disdu2_3*
120 Dispense Sequence c:\ACT13_28\R3-A.DSP with 1000ul to RB1_1to96 rack using NMP
121 Mix "RB1_1to96" for 2.00 minutes at 600 rpm(s) and wait.
122 Dispense Sequence c:\ACT13_28\R3-B.DSP with 1000ul to RB2_1to96 rack using NMP
123 Start mixing "RB1_1to96" for 2.00 minutes at 600 rpm(s) and continue.
124 Mix "RB2_1to96" for 2.00 minutes at 600 rpm(s) and wait.
125 Dispense Sequence c:\ACT13_28\R3-C.DSP with 1000ul to RB3_1to96 rack using NMP
126 Start mixing "RB1_1to96" for 2.00 minutes at 600 rpm(s) and continue.
127 Start mixing "RB2_1to96" for 2.00 minutes at 600 rpm(s) and continue.
128 Mix "RB3_1to96" for 2.00 minutes at 600 rpm(s) and wait.
129 Dispense Sequence c:\ACT13_28\R3-D.DSP with 1000ul to RB4_1to96 rack using NMP

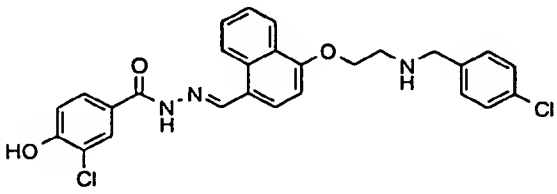
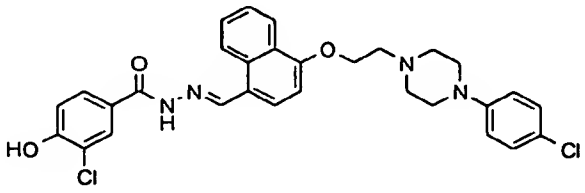
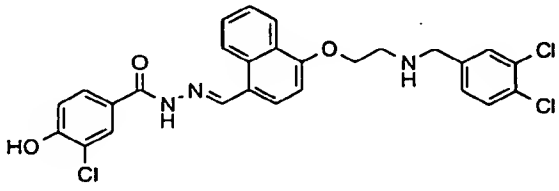
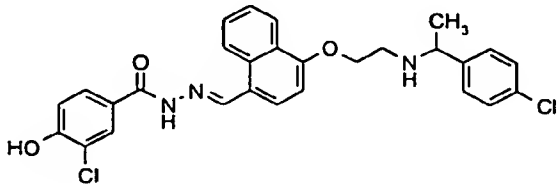
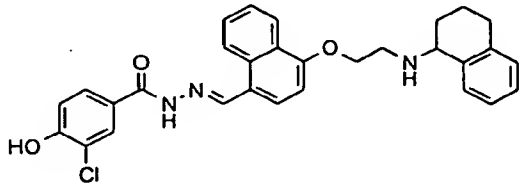
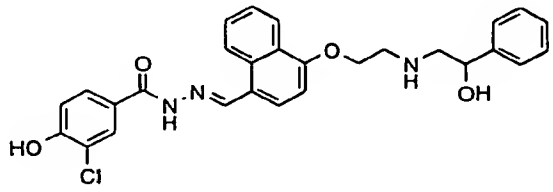
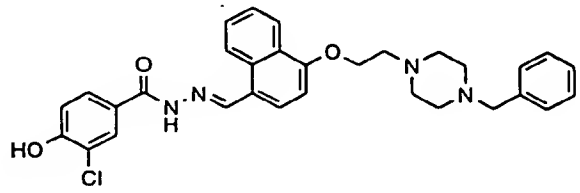
179 Pause
180 Dispense System Fluid Disdu1_4* 1500ul to RB1_1to96[1-96]
181 Dispense System Fluid Disdu1_4* 1500ul to RB2_1to96[1-96]
182 Dispense System Fluid Disdu1_4* 1500ul to RB3_1to96[1-96]
183 Dispense System Fluid Disdu1_4* 1500ul to RB4_1to96[1-96]
184 Start mixing "RB1_1to96" for 5.00 minutes at 600 rpm(s) and continue.
185 Start mixing "RB2_1to96" for 5.00 minutes at 600 rpm(s) and continue.
186 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s) and continue.
187 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
188 Empty RB1_1to96 for 5.000 minute(s)
189 Empty RB2_1to96 for 5.000 minute(s)
190 Empty RB3_1to96 for 5.000 minute(s)
191 Empty RB4_1to96 for 5.000 minute(s)
192
193 Repeat from step 180, 5 times
194
195 Dispense System Fluid Disdu1_4* 1500ul to RB1_1to96[1-96]
196 Dispense System Fluid Disdu1_4* 1500ul to RB2_1to96[1-96]
197 Dispense System Fluid Disdu1_4* 1500ul to RB3_1to96[1-96]
198 Dispense System Fluid Disdu1_4* 1500ul to RB4_1to96[1-96]
199 Start mixing "RB1_1to96" for 5.00 minutes at 600 rpm(s) and continue.
200 Start mixing "RB2_1to96" for 5.00 minutes at 600 rpm(s) and continue.
201 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s) and continue.
202 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s) and wait.
203 Wait for 25.000 minute(s)
204 Repeat from step 199, 1000 times
205
206 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3
207 Empty RB4_1to96 for 5.000 minute(s)
208 Pause
209
210 REM Clevage (50%TFA/DCM manually added, one rack at a time)
211 Flush Arm1 with Flush Diluter1, Arm2 with Flush Diluter 4
212 Mix "RB1_1to96" for 5.00 minutes at 600 rpm(s) and wait.
213 Wait for 5.000 minute(s)
214 Repeat from step 7, 5 times
215 Empty RB1_1to96 for 1 second(s)
216 Wait for 4 second(s)
217 Repeat from step 10, 25 times
218 Empty RB1_1to96 for 5.000 minute(s)
219
220 Dispense System Fluid Disdu1_4* 500ul to RB1_1to96[1-96]
221 Wait for 1.000 minute(s)
222 Empty RB1_1to96 for 1 second(s)
223 Wait for 4 second(s)
224 Repeat from step 17, 25 times
225 Empty RB1_1to96 for 5.000 minute(s)
226

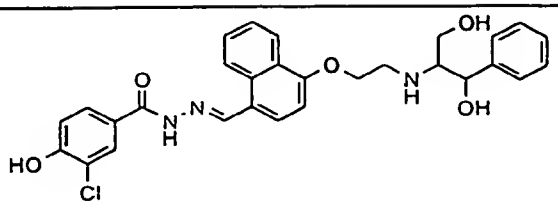
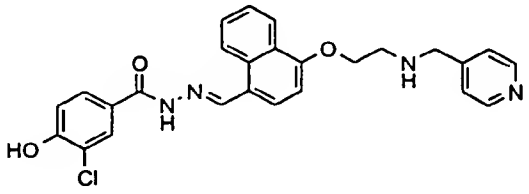
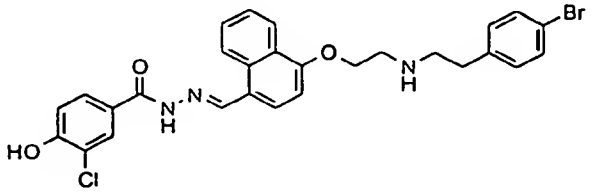
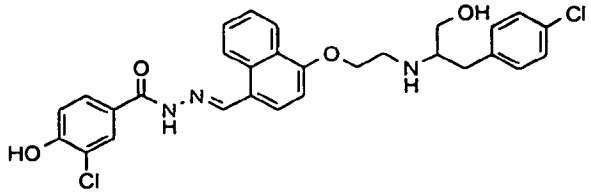
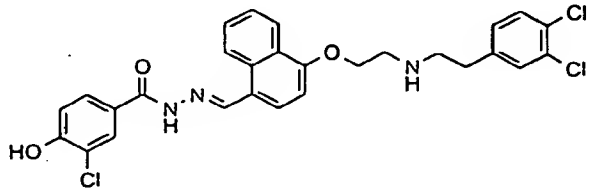
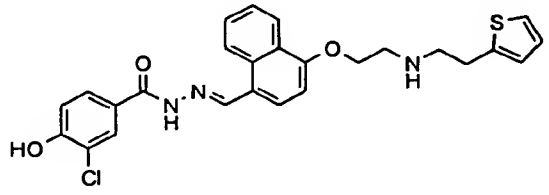
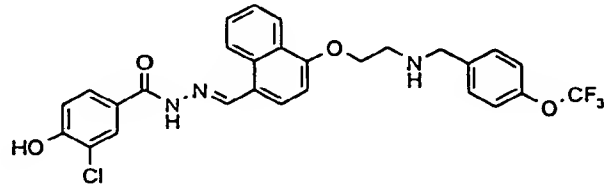
Ex No.	Structure	HPLC-MS (METHOD B) m/z	HPLC-MS (METHOD B) R_t (minutes)
702		596	15.9
703		522	8.82
704		502	6.62
705		488	6.68
706		543	10.93
707		522	9.40
708		494	7.87

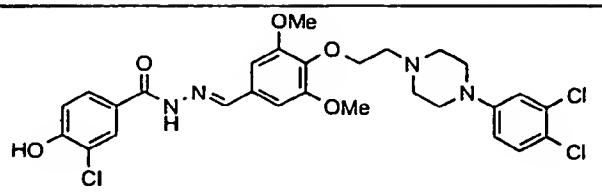
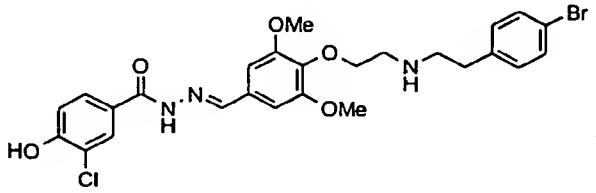
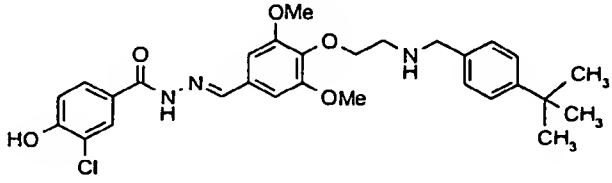
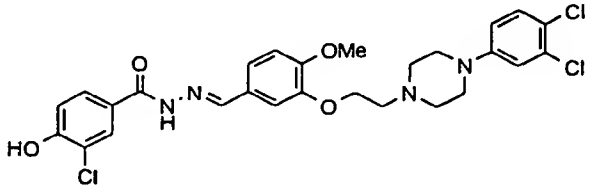
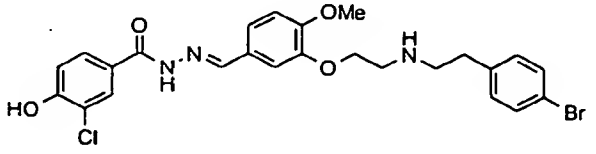
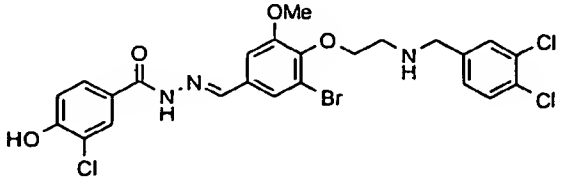
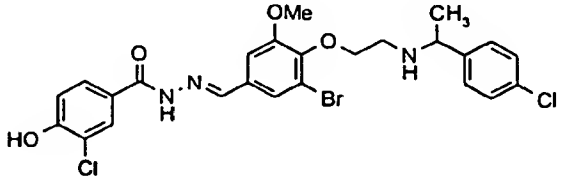
717		572	9.93
718		572	10.78
719		598	11.47
720		618	7.35
721		574	7.27
722		548	8.50

729		655	16.35
730		615	12.15
731		616	8.30
732		590	5.30
733		624	10.90
734		608	8.95

741		504	5.40
742		557	6.57
743		5.42	12.68
744		500	11.95
745		518	8.83
746		522	9.53
747		504	6.42

755		508	10.32
756		563	14.17
757		544	13.07
758		522	12.65
759		514	12.03
760		504	4.57
761		543	9.30

769		5.34	3.33
770		475	2.23
771		568	10.07
772		552	6.93
773		556	12.02
774		494	7.12
775		558	12.58

783		607	12.25
784		578	5.70
785		540	7.98
786		577	11.48
787		548	5.63
788		602	12.13
789		582	11.67

Found: C, 72.79%; H, 6.86%; N, 4.46%; C, 72.65%; H, 6.88%; N, 4.47%.

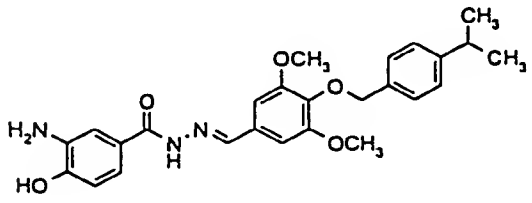
Methyl 3-amino-4-hydroxybenzoate (5.0 g, 30 mmol) was dissolved in ethanol (50 ml) and hydrazine hydrate (4.4 ml, 90 mmol) was added and the resulting mixture was heated at reflux temperature for 16 hours. After cooling the mixture was filtered and solid was washed with ethanol to afford after drying 1.4 g (28%) of 3-amino-4-hydroxybenzoic acid hydrazide as a solid. M.p.: 242 - 243 °C.

Calculated for $C_7H_9N_3O_2$: C, 50.30%; H, 5.43%; N, 25.14%.
Found: C, 50.27%; H, 5.46%; N, 24.35%; C, 50.41%; H, 5.47%; N, 24.38%.

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above 4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy]-2-methoxybenzaldehyde (93 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (2 x 4 ml) and dried by suction to afford 66 mg (48%) of the title compound as a solid. M.p.: 162 - 164 °C.

HPLC -MS (METHOD B): R_t = 6.50 minutes. m/z = 461.

EXAMPLE 793:
3-Amino-4-hydroxybenzoic acid [4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]-hydrazide



Syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) (10.2 g, 55 mmol) was dissolved in DMF (45 ml), and 4-isopropylbenzylchloride (9.7 g, 55 mmol) and potassium carbonate (11.5 g) were added successively. The resulting mixture was heated at 60 °C for 16 hours. After cooling, the mixture was partitioned between water (150 ml) and ethyl acetate (3 x 100 ml). The combined organic extracts were washed with water (100 ml), saturated NaCl (100 ml),

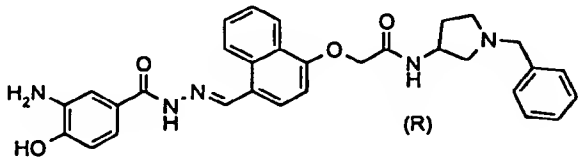
then partitioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from diethyl ether to afford 2.11 g (64%) (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide as a solid. M.p.: 98 - 101 °C.

Calculated for $C_{21}H_{24}N_2O_4.0.5H_2O$:
C, 66.83%; H, 6.68%; N, 7.42%.
Found:
C, 67.15%; H, 6.57%; N, 7.75%;
C, 66.96%; H, 6.57%; N, 7.77%.

The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (110 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (2 x 3 ml) and dried by suction to afford 109 mg (70%) of the title compound as a solid. M.p.: 157 - 160 °C.

HPLC-MS (METHOD B): R_t = 3.10 minutes. m/z = 518.

EXAMPLE 795:
(R)-2-{4-[(3-Amino-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



4-Hydroxy-1-naphthaldehyde (2.32 g, 13 mmol) was dissolved in DMF (7 ml) and potassium carbonate (6.2 g, 45 mmol) was added followed by a suspension of the above (3R)-N-(1-Benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.0 g, 9 mmol) in DMF (16 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then parti-

(5 ml) was added at room temperature. The mixture was stirred at room temperature for 16 hours. The mixture was filtered, washed with dichloromethane and dried in vacuo to afford 7.3 g (64%) of (3S)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride as a solid which was used directly in the next step.

4-Hydroxy-2-methoxybenzaldehyde (2.39 g, 16 mmol) was dissolved in DMF (10 ml) and potassium carbonate (7.3 g, 52 mmol) was added followed by a suspension of the above (3S)-N-(1-benzylpyrrolidin-3-yl)-2-bromoacetamide hydrochloride (3.5 g, 10 mmol) in DMF (20 ml). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then partitioned between water (100 ml) and ethyl acetate (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were washed with saturated sodium chloride (3 x 15 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue (4 g) was crystallised from a mixture of diethyl ether and heptane, filtered and dried in vacuo to afford 2.7 g (71%) (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)-acetamide as a solid. M.p.: 96 - 100 °C.

Calculated for $C_{21}H_{24}N_2O_4.0.25H_2O$:
C, 67.63%; H, 6.62%; N, 7.51%.
Found:
C, 67.35%; H, 6.61%; N, 7.85%;
C, 67.24%; H, 6.59%; N, 7.82%.

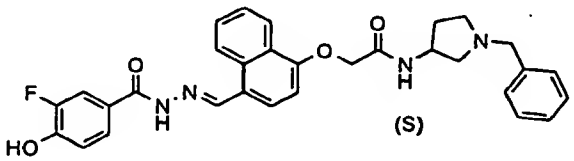
The above 3-amino-4-hydroxybenzoic acid hydrazide (50 mg, 0.3 mmol) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (110 mg, 0.3 mmol) were dissolved in 2-propanol (4 ml) and the mixture was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the precipitate was washed with 2-propanol (6 x 2 ml) and dried by suction to afford 109 mg (70%) of the title compound as a solid. M.p.: 139 - 141 °C.

HPLC-MS (METHOD B): R_t = 3.15 minutes. m/z = 518.

EXAMPLE 797:

EXAMPLE 798:

(S)-2-{4-[(3-Fluoro-4-hydroxybenzoyl)hydrazonomethyl]naphthyl-1-yloxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



This compound was prepared on solid phase using resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide, prepared similarly as described above for the resin bound 3-chloro-4-hydroxybenzoic acid hydrazide. Thus, methyl 3-fluoro-4-hydroxybenzoate was attached to the resin. Hydrolysis of the methyl ester (aq. LiOH, dioxane, 60 °C) followed by reaction with hydrazine (PyBOP, hydrazine, DMF) afforded resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide.

The resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) was swelled in DMF (10 ml) for 30 minutes and filtered. This was repeated once more. DMF (4 ml) and the above (S)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formylnaphthyl-1-yloxy)acetamide (0.4 g, 0.94 mmol) were added followed by triethyl orthoformate (1.5 ml) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with DMF (5 x 4 ml) and dichloromethane (5 x 4 ml). The compound was cleaved off the resin by addition of 50% TFA in dichloromethane (6 ml) and shaking at room temperature for 1 hour. Filtration followed by extraction of the resin with a mixture of methanol and dichloromethanne (4:6) (2 x 4 ml) followed by extraction with dichloromethane (4 ml). The combined filtrates were concentrated in vacuo, stripped successively with wet methanol, dichloromethane, methanol and dichloromethane. The residue (0.39 g) was purified by column chromatography on silica gel (40 g) eluting first with a mixture of dichloromethane, ethanol and 25% aq. ammonia (90:9:1), then with (85:13.5:1.5) and finally with (80:18:2). Pure fractions were pooled and concentrated in vacuo to afford 0.15 g of the title compound.

HPLC-MS (METHOD B): R_t = 8.82 minutes. m/z = 541.

Calculated for $C_{31}H_{29}N_4O_4F.0.25CH_2Cl_2$:

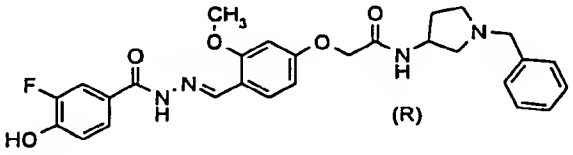
C, 66.81%; H, 5.29%; N, 9.97%. Found: C, 67.30%; H, 5.48%; N, 10.03%;

cleavage the compound was purified by column chromatography to afford 0.13 g of the title compound.

HPLC-MS (METHOD B): R_t = 3.68 minutes. m/z = 521.

Calculated for $C_{28}H_{29}N_4O_5F.0.25CH_2Cl_2$:
C, 62.63%; H, 5.49%; N, 10.34%.
Found:
C, 62.92%; H, 5.83%; N, 10.15%;
C, 62.71%; H, 5.81%; N, 10.16%.

EXAMPLE 801:
(R)-2-{4-[(3-Fluoro-4-hydroxybenzoyl)-hydrazonomethyl]-3-methoxyphenoxy}-N-(1-benzylpyrrolidin-3-yl)acetamide



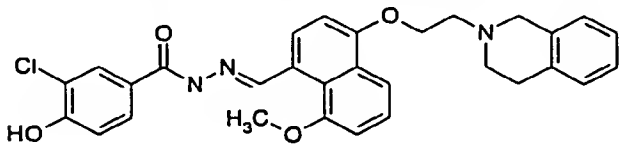
This compound was prepared similarly as described in the previous example starting from resin bound 3-fluoro-4-hydroxybenzoic acid hydrazide (1 g, 0.94 mmol) and the above (R)-N-(1-benzylpyrrolidin-3-yl)-2-(4-formyl-3-methoxyphenoxy)acetamide (0.4 g, 0.94 mmol). After cleavage the compound was purified by column chromatography to afford 0.16 g of the title compound.

HPLC-MS (METHOD B): R_t = 4.18 minutes. m/z = 521.

Calculated for $C_{28}H_{29}N_4O_5F.0.25CH_2Cl_2$:
C, 62.63%; H, 5.49%; N, 10.34%.
Found:
C, 62.65%; H, 5.73%; N, 10.31%;
C, 62.84%; H, 5.81%; N, 10.30%.

EXAMPLE 802:

3-Chloro-4-hydroxy-benzoic acid {4-[2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)-ethoxy]-8-methoxy-naphthalen-1-ylmethylene}-hydrazide



4-hydroxy-8-methoxynaphthalene-1-carbaldehyde (1 g, 5 mmol) was dissolved in DMF (15 mL). To this mixture potassium carbonate (3.4 g, 25 mmol) and 1,2-dibromoethane (4 mL, 50 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. Water (150 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 90 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried ($MgSO_4$) and evaporated in vacuo to afford 1.13 g (74%) of 4-(2-bromoethoxy)-8-methoxynaphthalene-1-carbaldehyde.

HPLC-MS (Method A): R_t = 14.1 minutes. m/z = 309.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H = 3.99 (3H, s), 7.00 (1H, d), 7.20 (1H, d), 7.47 (1H, t), 7.88 (2H, m), 10.9 (1H, s).

The above resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (2 g, 1.8 mmol) was swelled in DMF (25 mL) for 30 minutes and the above 4-(2-bromoethoxy)-8-methoxynaphthalene-1-carbaldehyde (1.7 g, 5.4 mmol) was added followed by triethyl orthoformate (1.2 mL) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with DMF (3 x 25 mL), dichloromethane (4 x 25 mL) and N-methyl pyrrolidin-2-one (NMP) (2 x 25 mL). NMP (25 mL) was added followed by potassium iodide (0.6 g) and 1,2,3,4-tetrahydro-isoquinoline (2.25 mL, 18 mmol) and the resulting mixture was shaken at room temperature for 16 hours. The mixture was filtered and the resin was successively washed with NMP (2 x 25 mL) and dichloromethane (6 x 25 mL). The compound was cleaved off the resin by addition of 50% TFA in dichloromethane (30 mL) and shaking at room temperature for 1 hour. After filtration followed by extraction of the resin with dichloromethane (2 x 30 mL) the combined filtrates were concentrated in vacuo. The residue was partitioned between ethyl acetate (80 mL) and saturated sodium hydrogen carbonate (100 mL). The aqueous phase was extracted with

General Procedure for Examples 804 to 824:

The compounds were prepared as single entities according to the following equation

Resin——[Building block 1] ⟶

Resin——[Building block 1]——[Building block 2] ⟶

Resin——[Building block 1]——[Building block 2]——[Building block 3]

and were simultaneously deprotected (when required) and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

[Building block 1]——[Building block 2]——[Building block 3].

The following compounds were prepared as single entities by parallel synthesis on a solid support. Preparation of Resin-[Building block 1] and attachment of [Building block 2] was done manually, whereas the attachment of [Building block 3] and cleavage from the resin were performed on an Advanced ChemTech Model 496 HTS in several runs.

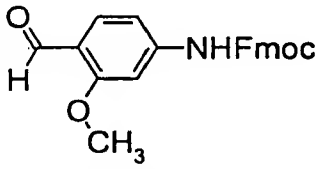
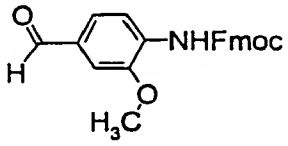
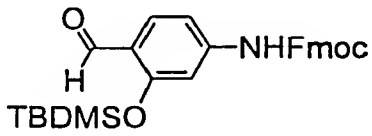
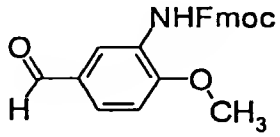
The starting resin, Resin-[Building block 1], was prepared as described above.

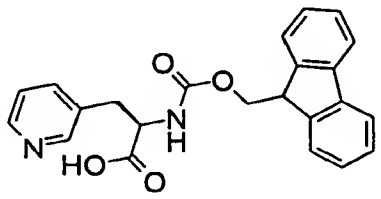
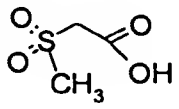
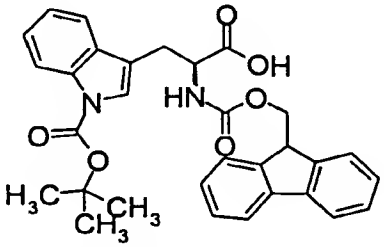
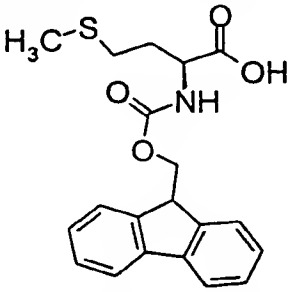
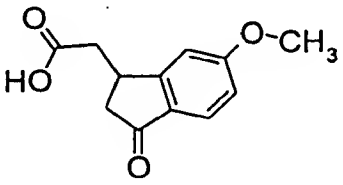
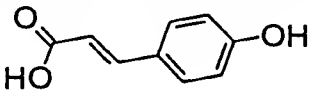
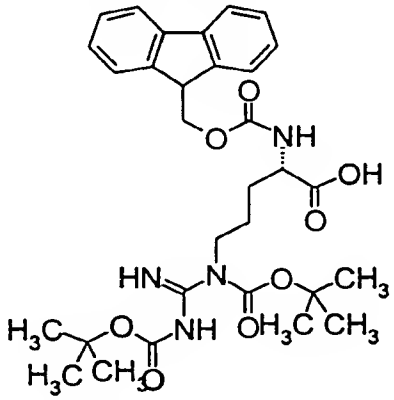
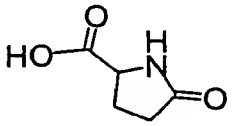
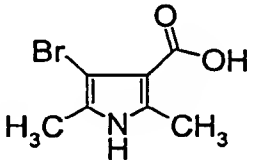
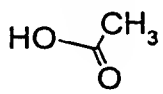
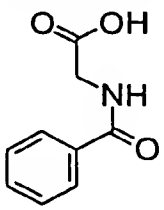
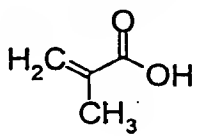
The resin used was a polystyrene resin with a Wang linker and the substitution capacity was 0.9 mmol/g.

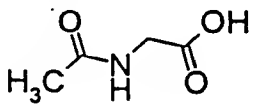
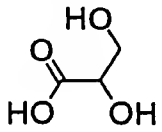
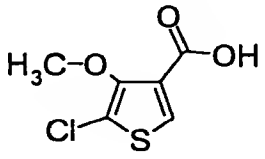
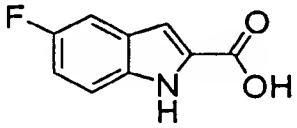
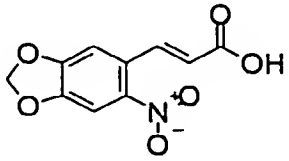
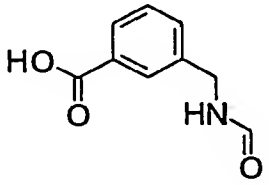
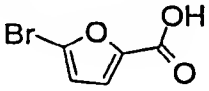
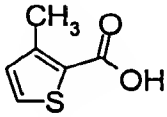
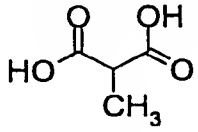
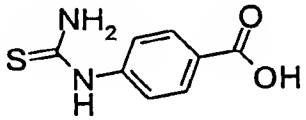
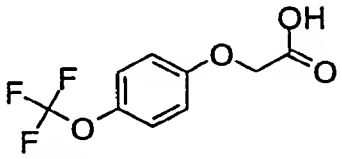
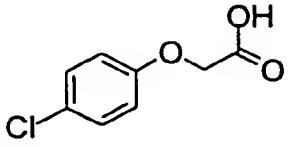
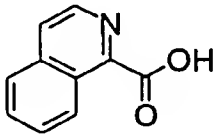
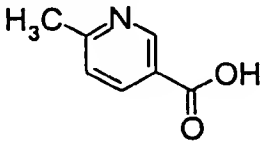
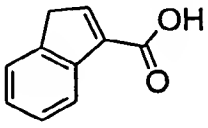
All compounds are based on successive attachment of [Building block 2] and [Building block 3] to Resin-[Building block 1] in a combinatorial way according to the following formulae, which are included in the general formula II:

The following building blocks were used:

[Building block 2]:

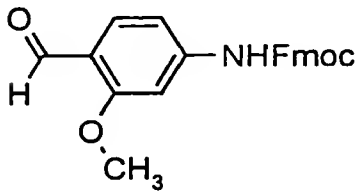
(4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester: 	(4-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester 
3-(tert-Butyldimethylsilanyloxy)-4-formylphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester: 	(5-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester: 

Foc-beta-(3-pyridyl)-D-Ala-OH 	Methanesulfonylacetic acid 	Fmoc-Trp(Boc)-OH 
Fmoc-L-Methionine 	5-Methoxy-1-indanone-3-acetic acid 	4-Hydroxycinnamic acid 
Fmoc-Arg(Boc)-2-OH 	5-Oxopyrrolidine-2-carboxylic acid 	4-Bromo-2,5-dimethyl-1-H-pyrrole-3-carboxylic acid 
Acetic acid 	Hippuric acid 	2-Methylpropenoic acid 

N-Acetylglycine 	DL-Glyceric acid 	2-Chloro-3-methoxythiophene-4-carboxylic acid 
5-Fluoroindole-2-carboxylic Acid 	3-(4,5-Methylenedioxy-2-nitrophenyl)acrylic acid 	3-(Formylaminomethyl)benzoic acid 
5-Bromo-2-furoic Acid 	3-Methylthiophene-2-carboxylic acid 	Methylmalonic acid 
4-Thioureido-benzoic acid 	(4-Trifluoromethoxy)phenoxy acetic acid 	(4-Chlorophenoxy)acetic acid 
Isoquinoline-1-carboxylic a-cid 	6-Methylnicotinic acid 	3H-Indene-1-carboxylic acid 

Preparation of [Building block 2]:

(4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



Methyl 4-amino-2-methoxybenzoate (14.7 g, 7.3 mmol) and Fmoc-Osu (26.1 g, 77.3 mmol) were stirred in a mixture of acetonitrile and water (1:1, 320 mL) at reflux for 16 hr. The reaction mixture was concentrated to half the volume and the precipitate isolated by filtration. The isolated solid was dissolved in ethyl acetate (300 mL) and washed with 0.4 N hydrochloric acid (200 mL), 0.2 N hydrochloric acid (200 mL), water (200 mL) and a 20 % saturated solution of sodium chloride (200 mL). After drying (magnesium sulphate) the organic phase was concentrated in vacuo, and the solid residue was washed with methanol and dried.

The crude product (12g) was dissolved in dichloromethane (1 L) under nitrogen and a solution of diisobutylaluminium hydride (90 mL, 1.2 M in toluene) was dropwise added at 0-5°C. The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (58 mL) at 0-5 °C. The reaction mixture was stirred at 20°C for 3 hr and filtered. The filtrate was concentrated in vacuo. The crude product (6.8 g) was suspended in dichloromethane (400 mL) and manganese dioxide (15.6 g, 180 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give 5.1 g of the title compound.

m.p. 187-188°C

HPLC-MS (METHOD A): R_t = 15.1 min, m/z= 374.

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

found: C, 73.44; H, 5.20; N, 3.56%

(4-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:

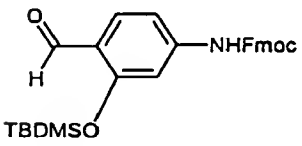
m.p. 150-152°C

HPLC (Method 1) R_t = 30.6 min

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

found: C, 73.54; H, 5.18; N, 3.65%

3-(tert-Butyldimethylsilanyloxy)-4-formylphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



4-(9H-Fluoren-9-ylmethoxycarbonylamino)-2-hydroxybenzoic acid methyl ester:

Thionylchloride (19.4g, 163 mmol) was dropwise added to an ice cold solution of 4-amino salicylic acid (10.0g, 65.3 mmol) in methanol (200 mL). The reaction mixture was hereafter heated to 65°C for 6 days. The reaction mixture was concentrated in vacuo and the crude product was dissolved in a mixture of acetonitrile and water (1:1, 220 mL). Fmoc-Osu (22.0 g, 65.3 mmol) was added and the reaction mixture was stirred at 90°C for 16 hr. The reaction mixture was concentrated to 100 mL in vacuo, and water (50 mL) and ethyl acetate (250 mL) added. The organic phase was isolated and washed with water (2x50 mL), a saturated solution of sodium chloride (2x50 mL), dried (magnesium sulphate) and concentrated in vacuo.

The residue was purified on silica (300 g) using ethyl acetate and n-heptane (1:2) as eluent. The product was recrystallized from methanol to give 4-(9H-fluoren-9-ylmethoxycarbonylamino)-2-hydroxybenzoic acid methyl ester.

m.p.156-9°C

HPLC (Method 1) R_t = 31.7 min

Micro analysis: calculated: C, 70.94; H, 4.92; N, 3.60%

found: C, 70.73; H, 4.98; N, 3.37%

(magnesium sulphate) and concentrated in vacuo. The crude product (7.7 g) and Fmoc-Osu (12.9 g, 38.2 mmol) were stirred in a mixture of acetonitrile and water (1:1, 75 mL) at 20°C for 16 hr, and at reflux for 3.5 hr. The reaction mixture was concentrated to half the volume and the precipitate isolated by filtering the mixture to give 15 g of intermediate crude product.

The product (5 g, 12 mmol) was dissolved in dichloromethane (400 mL) under nitrogen and a solution of diisobutylaluminium hydride (38 mL, 1.2M in toluene) was dropwise added at 0-5°C. The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (23 mL) at 0-5°C. The reaction mixture was stirred at 20°C for 1.5 hr and filtered. The filtrate was concentrated in vacuo to give 4.9 g of intermediate product. The product (4.9 g) was suspended in dichloromethane (180 mL) and manganese dioxide (11.2 g, 129 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give 4.3 g crude product that was purified on silica (150 g) using ethyl acetate and n-heptane (3:7) as eluent to give 1.9 g of the title compound.

m.p. 139-142°C

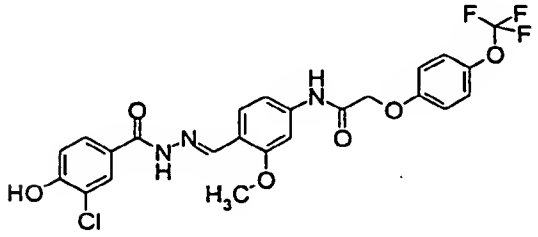
HPLC (Method 1) R_t = 29.8 min

Micro analysis: calculated: C, 73.98; H, 5.13; N, 3.75%

found: C, 73.45; H, 5.17; N, 3.72%

EXAMPLE 804:

N-(4-[3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)-2-(4-trifluoromethoxyphenoxy)acetamide



Further, a library of compounds of all the possible combinations of the above listed building blocks ([building block 1], [building block 2] and [building block 3]) was prepared in parallel as individual entities analogously to the previous example on an Advanced ChemTech Model 384 HTS using the following ChemFile to control the operation of the synthesizer. The compounds are all expected to be present in the respective wells.

The four [building block 2] aldehydes, (4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, (4-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, 3-(tert-Butyldimethylsilanyloxy)-4-formylphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester and (5-Formyl-2-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, were coupled to four individually batches of the resin bound 3-chloro-4-hydroxybenzoic acid hydrazide (resin-[building block 1]) using the same procedure as described for step 1 in the example above. Subsequently the Fmoc deprotection of the anilino group was carried out as described in step 2 in the example above.

The four different examples of resin[building block 1][building block 2] thus prepared were equally distributed in the wells in the synthesizer prior to the initialization of the device. The attachment of the array of [building block 3] mentioned above was carried out in a fully combinatorial way with the four types of resin[building block 1][building block 2] using the general procedure as described in step 3 in the example above. The final cleavage was performed using the same general procedure as described in step 4 in the example above. During this cleavage step deprotection of acid sensible protection groups was also taken place. These two steps 3 and 4 were carried out (in several runs) on an ACT 496 HTS automated synthesizer using the following ChemFile to control the device.

ChemFile: C:\DATA\90250017.CHM

```
1 Empty RB1to96 for 2.000 minute(s)
2 Flush  Arm1 with NMParm1 and DCMarm1
3
4 REM Adding acids 1 to 36
5
```

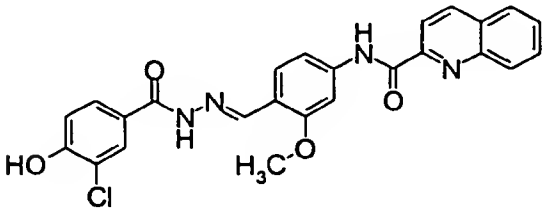
55 Mix for 3.00 minutes at 600 rpm(s)
56 Empty RB1to96 for 3.000 minute(s)
57 Repeat from step 54, 2 times
58 Flush Arm1 with NMParm1 and DCMarm1, Arm2 with DCMarm2
59 Dispense System Fluid DCMdualarm* 1000ul to RB1to96[1-96]
60 Mix for 3.00 minutes at 600 rpm(s)
61 Empty RB1to96 for 3.000 minute(s)
62 Repeat from step 59, 5 times
63
64 REM TFA CLEAVAGE
65
66 Mix for 1.00 minutes at 300 rpm(s)
67 Transfer 1000ul from Reagent2[1]() to RBcleavage1to96[1-96] using DCMarm1
68 Mix for 1.00 hours at 600 rpm(s)
69 Empty RBcleavage1to96 for 30 second(s)
70 Dispense System Fluid DCMdualarm* 500ul to RBcleavage1to96[1-96]
71 Mix for 5.00 minutes at 300 rpm(s)
72 Empty RBcleavage1to96 for 30 second(s)
73

Dispense sequence files C:\act\ACID1-36.DSP are subroutines that control the combinatorial addition of the amines into the 4 reaction blocks each containing 96 wells in the syntheziser.

Examples of compounds from this library were characterized by HPLC-MS (molecular mass & retention time) and includes:

EXAMPLE 805:

Quinoline-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



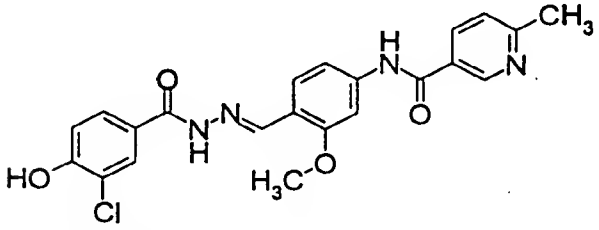
m.p. 236-238°C

HPLC (Method 1) R_t=26.2 min

EXAMPLE 806:

EXAMPLE 809:

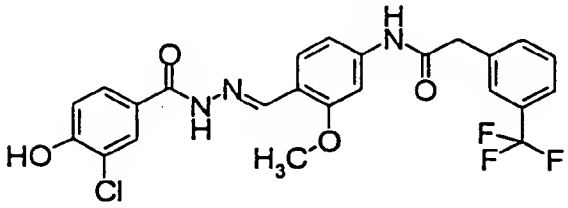
N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-6-methylnicotinamide



HPLC-MS (METHOD A) R_t=8.2 min, m/z=439

EXAMPLE 810:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-trifluoromethylphenyl)acetamide



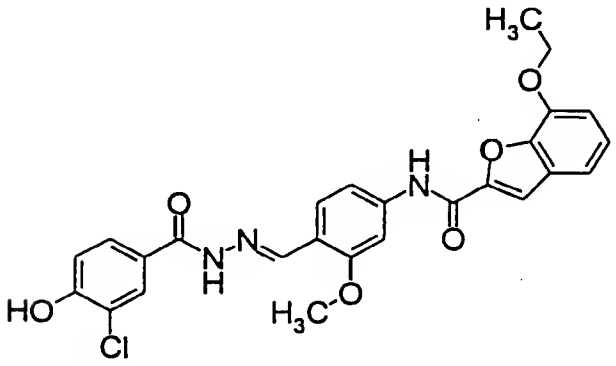
HPLC-MS (METHOD A) R_t=13.4 min, m/z=506

EXAMPLE 811:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2,4-dichlorophenoxy)acetamide

EXAMPLE 814:

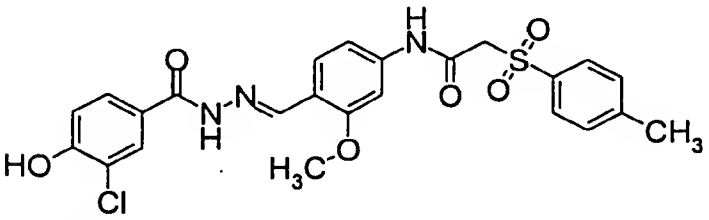
7-Ethoxybenzofuran-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



HPLC-MS (METHOD A) R_t=13.3 min, m/z=508

EXAMPLE 815:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(toluene-4-sulonyl)acetamide



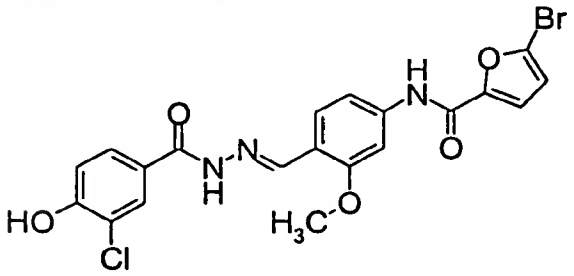
HPLC-MS (METHOD A) R_t=10.8 min, m/z=517

EXAMPLE 816:

Benzofuran-2-carboxylic acid {4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-amide

EXAMPLE 819:

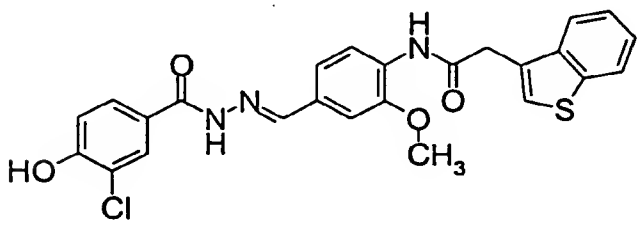
5-Bromofuran-2-carboxylic acid {4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



HPLC-MS (METHOD A) R_t=11.4 min, m/z=494

EXAMPLE 820:

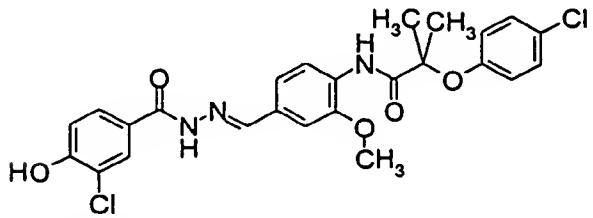
2-Benzo[b]thien-3-yl-N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}acetamide



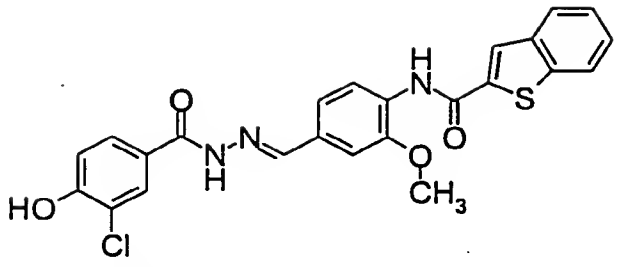
HPLC-MS (METHOD A) R_t=13.4 min, m/z=494

EXAMPLE 821:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-2-methoxyphenyl}-2-(4-chlorophenoxy)-2-methylpropionamide



HPLC-MS (METHOD A) R_t=14.7 min, m/z=516



HPLC-MS (METHOD A) R_t=13.8 min, m/z=480

HPLC Method 1.

The RP-HPLC analysis was performed using UV detection at 254 nm and a Merck Hibar LiChrosorb RP-18 (5 µm) prepacked column (Cat. No. 50333), which was eluted at 1 mL/minute. Two solvent systems were used:

Solvent system I: 0.1% Trifluoroacetic acid in acetonitrile. Solvent system II: 0.1% Trifluoroacetic acid in water.

The column was equilibrated with a mixture composed of 20% of solvent system I and 80% of solvent system II. After injection of the sample a gradient of 20% to 80% of solvent system I in solvent system II was run over 30 minutes. The gradient was then extended to 100% of solvent system I over 5 minutes followed by isocratic elution with 100% of this system for 6 minutes.

General Procedure for Examples 825 to 875:

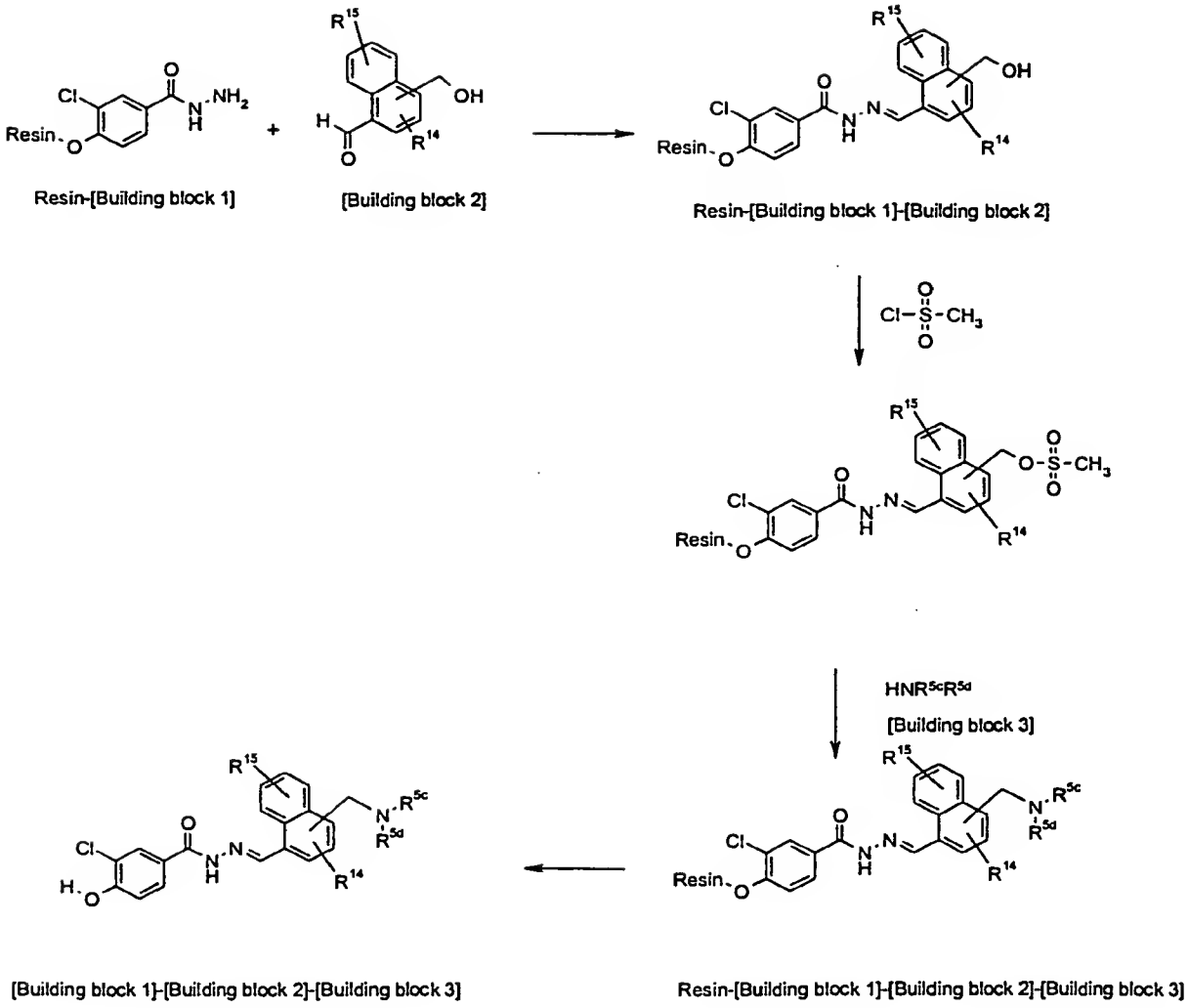
The compounds were prepared as single entities according to the following equation

Resin——[Building block 1] ⟶

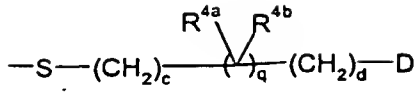
Resin——[Building block 1]——[Building block 2] ⟶

Resin——[Building block 1]——[Building block 2]——[Building block 3]

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula

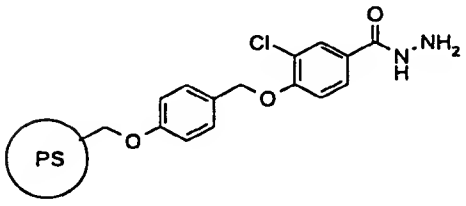

Resin-[Building block 1]
[Building block 2]
Resin-[Building block 1]-[Building block 2]
HNR5cR5d
[Building block 3]
Resin-[Building block 1]-[Building block 2]-[Building block 3]
[Building block 1]-[Building block 2]-[Building block 3]

and

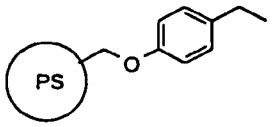


where R^{4a}, R^{4b}, c, q, d, and D are as defined for formula I or -D' where -D' is defined as a subset of -D that contains a thiol that can react as a nucleophile.

The following resin, here depicted as Resin-[Building block 1] was used:



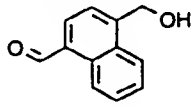
where PS is polystyrene. In the following "Resin" is the polystyrene resin with the Wang linker:



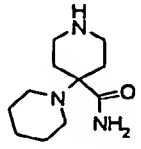
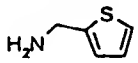
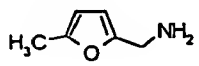
= Resin

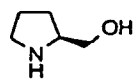
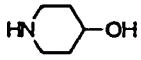
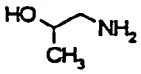
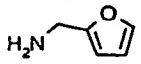
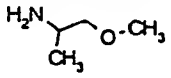
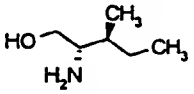
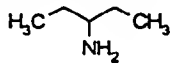
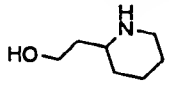
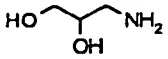
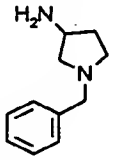
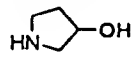
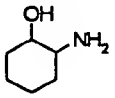
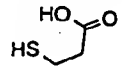
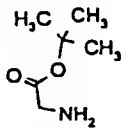
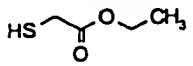
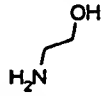
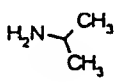
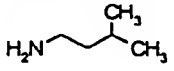
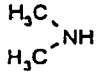
The following building blocks were used:

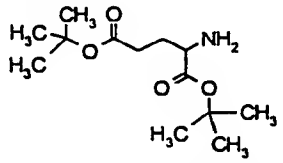
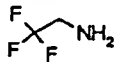
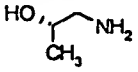
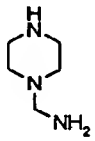
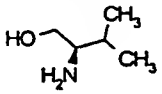
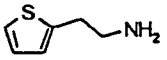
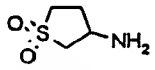
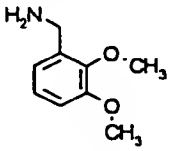
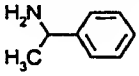
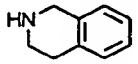
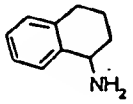
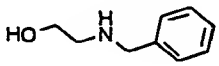
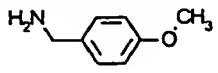
[Building block 2]:

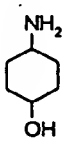
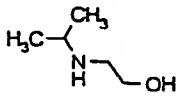
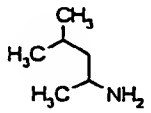
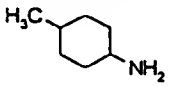
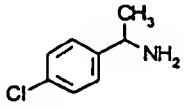
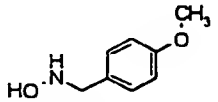
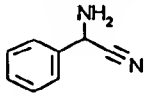
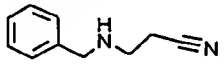
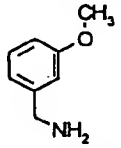
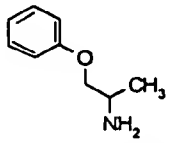
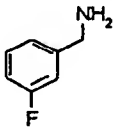
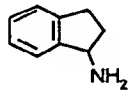
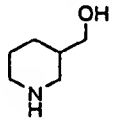
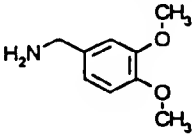
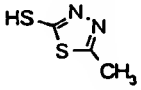
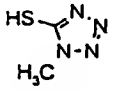
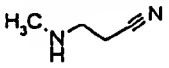
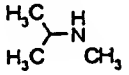
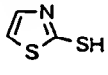
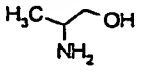
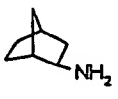
4-Hydroxymethylnaphthalene-1-  carbaldehyde

[Building block 3]:

(1,4'-Bipiperidine)-4'carboxamide 	2-Thiophenemethylamine 	5-Methyl-2-furanmethylamine 

L-Prolinol 	4-Hydroxypiperidine 	1-Amino-2-propanol 
Furfurylamine 	2-Methoxyisopropylamine 	L-Isoleucinol 
3-Aminopentane 	2-Piperidineethanol 	3-Amino-1,2-propanediol 
Cyclopropylamine 	Ethylenediamine 	1-Benzyl-3-Aminopyrrolidine 
3-Pyrrolidinol 	2-Aminocyclohexanol 	Morpholine 
3-Mercaptopropionic acid 	Glycine tert butylester 	3-Mercaptopropionic acid ethyl ester 
Ethylamine 	Methylamine 	2-Aminoethanol 
Isopropylamine 	Isopentylamine 	Dimethylamine 

Glutamic Acid di tert butyle-ster 	2,2,2-Trifluoroethylamine 	S-1-amino-2-propanol 
4-(Aminomethyl)-piperidine 	D-Valinol 	Thiophene-2-ethylamine 
Tetrahydro-3-thiophenamine 1,1-dioxide 		
2,3-Dimethoxybenzylamine 	Alfa-methylbenzylamine 	1,2,3,4-Tetrahydroisoquinoline 
1,2,3,4-Tetrahydro-1-naphthylamine 	N-Benzylethanolamine 	4-Methoxybenzylamine 

4-Aminocyclohexanol 	2-Isopropylaminoethanol 	1,3-Dimethylbutanamine 
4-Methylcyclohexylamine 	Alfa-methyl-4-chlorobenzyl-amine 	4-Methoxybenzylhydroxyl-amine 
2-Phenylglycinonitrile 	3-(Benzylamino)propionitrile 	3-Methoxybenzylamine 
1-Methyl-2-phenoxyethylamine 	3-Fluorobenzylamine 	1-Aminoindan 
3-Piperidinemethanol 	3,4-Dimethoxybenzylamine 	2-Mercapto-5-methylthiadiazole 
1-Methyl-5-mercaptotetra-zole 	3-Methylaminopropionitril 	Isopropylmethylamine 
2-Mercaptothiazole 	2-Amino-1-propanol 	exo-2-Aminonorbornane 

Preparation of resin-[Building block 1]:

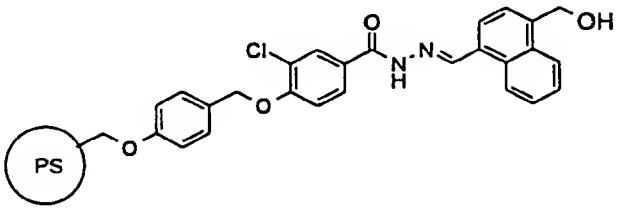
This resin was prepared as described above.

Preparation of 4-hydroxymethylnaphtaldehyde ([Building block 2]):

The preparation of this compound is described above.

Preparation of resin-[Building block 1]-[Building block 2]:

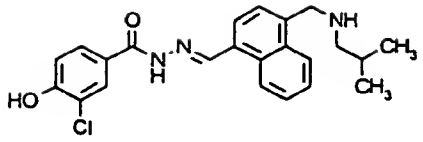
Preparation of resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide:



Resin-[Building block 1] (4 g) was suspended in DMF (40 mL) and was allowed to swell for 15 min. and then washed with DMF (2 x 40 mL), DCM (3 x 40 mL) and DMSO (2 x 40 mL). The solvent was removed by filtration. 1.488 g (8 mmol) 4-hydroxymethylnaphtaldehyde was dissolved in 40 mL DMSO and was added to the resin followed by 4 mL glacial acetic acid. The suspension was shaken for 16 hours at 25 °C. The resin was successively washed with DMSO (2 x 40 mL), THF (3 x 40 mL), CH_3OH (40 mL), CH_2Cl_2 (40 mL), CH_3OH (40 mL), CH_2Cl_2 (40 mL) and dried in vacuo at 40 °C for 16 hours to afford resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide.

EXAMPLE 825:

3-chloro-4-hydroxybenzoic acid (4-(1H-1,2,4-Triazol-3-ylsulfanylmethyl)naphthyl-methylene)hydrazide

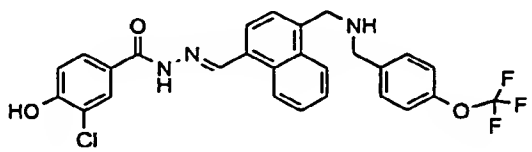


The resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthyl-methylene)hydrazide (resin-[Building block 1]-[Building block 2]) (50 mg, ~ 0.05 mmoles) was swelled in CH_2Cl_2 (1 mL) for 15 min, then washed with CH_2Cl_2 (2 x 0.5 mL). 0.4 mL CH_2Cl_2 and 0.4 mL diisopropylethylamine was subsequently added and the suspension was cooled to 0 °C. Methanesulfonylchloride (0.1 mL) was dissolved in CH_2Cl_2 (0.3 mL) and added to the suspension. The mixture was allowed to react at 0 °C for 30 min, then at 25 °C for 1 hour. The resin was isolated by filtration and washed with CH_2Cl_2 (2 x 0.5 mL) and DMSO (0.5 mL). DMSO (0.5 mL) was added followed by 50 µL isobutylamine and 100 µL diisopropylethylamine. The mixture was shaken at 25 °C for 16 hours, filtered and washed successively with DMSO (2 x 0.5 mL), THF (3 x 0.5 mL), CH_3OH (0.5 mL), CH_2Cl_2 (0.5 mL), CH_3OH (0.5 mL), CH_2Cl_2 (4 x 0.5 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a 50% solution of trifluoroacetic acid in CH_2Cl_2 (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH_3OH (0.5 mL) and acetonitrile (0.5mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B): R_t = 4.20 min; m/z = 410 (M+1)

EXAMPLE 826:

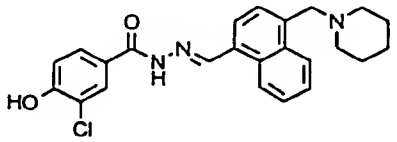
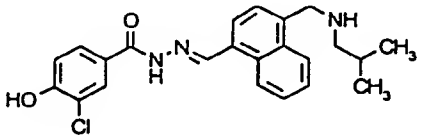
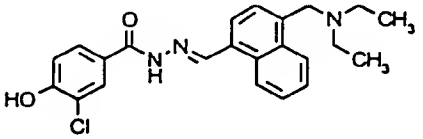
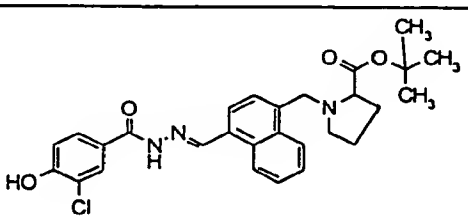
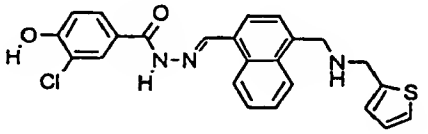
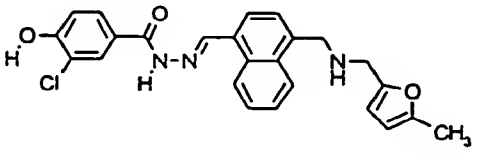
3-Chloro-4-hydroxybenzoic acid ((4-(4-trifluoromethoxybenzylamino)methyl)naphthyl-methylene)hydrazide

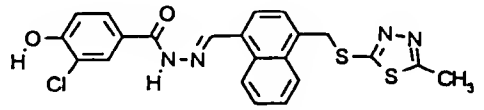
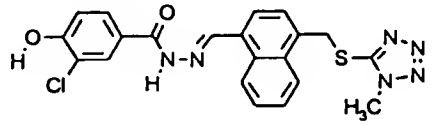
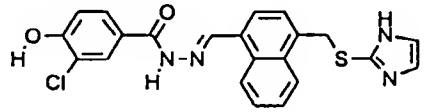
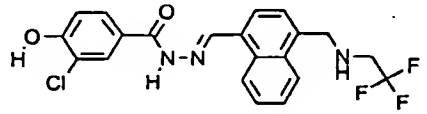
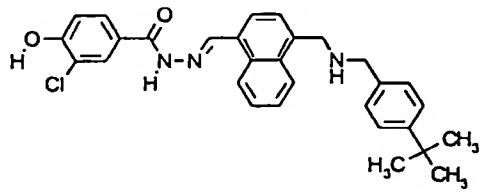


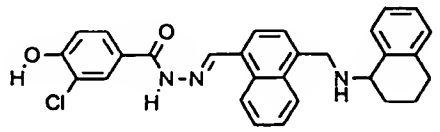
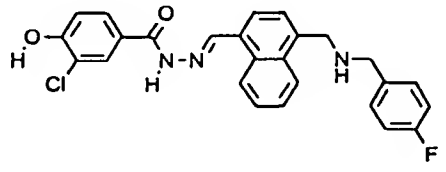
Resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide: (resin-[building block 1]-[building block 2]) (50 mg) was swelled in a 1:1 mixture of CH_2Cl_2 and N-methyl-2-pyrrolidone (0.5 mL) for 15 minutes and then washed with CH_2Cl_2 (3 x 0.5 mL). 800 µL of a 1:1 mixture of CH_2Cl_2 and diisopropylethylamine was added to the resin

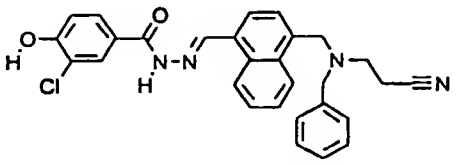
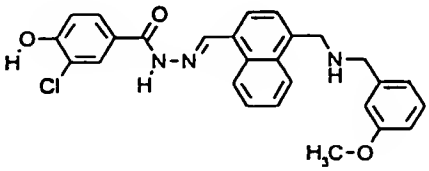
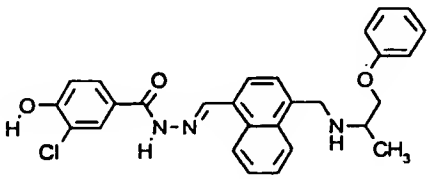
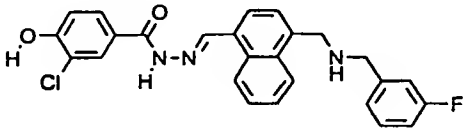
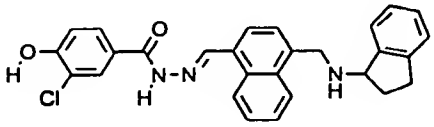
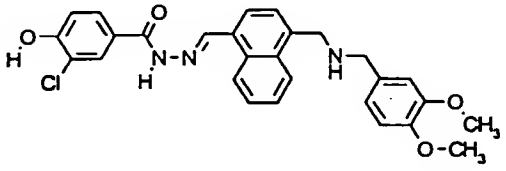
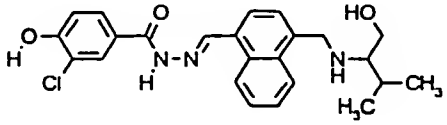
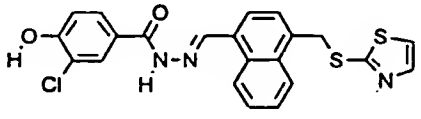
2 REM via mesylation
3
4 .
5 REM Dipense resin bound benzylic alchohol to wells
6
7
8 REM Setup Diluter1=DCM, D2=NMP (N-methyl-2-pyrrolidone), D3=NMP, D4=DCM
9 REM Adjust pressure
10 REM Add 100 mL DIEA/DCM 1:1 mixture to Reagent1
11 REM Add 70 mL MsCl/DCM 1:3 mixture to Reagent2
12 REM Add 100 mL TFA/DCM 1:1 mixture to Reagent3
13 REM Add 100 mL CH3CN to Reagent4
14 REM Nitrogen for cooling
15
16 Pause
17 REM Initialising...
18
19 REM Subroutine Empty1_72_3min is called twice to remove DCM/NMP from dispensed resin
20 Go to ChemFile MTY72_3M.CHM, line 1
21 Go to ChemFile MTY72_3M.CHM, line 1
22
23 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and with Flush Diluter 4
24
25 REM Washing with DCM, 3 times
26 Dispense System Fluid Disdu1_4* 500ul to RB1_1to96[1-72]
27 Mix "RB1_1to96" for 3.00 minutes at 300 rpm(s) and wait.
28 REM Subroutine Empty1_72_3min
29 Go to ChemFile MTY72_3M.CHM, line 1
30 Repeat from step 26, 2 times
31
32 REM Adding DCM/DIEA mixture from Reagent1
33 Transfer 800ul from REAGENT_1[1](DCM/DIEA) to RB1_1to96[1-72] using Flush Diluter1
34 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
35 Set Temperature of rack "RB1_1to96" to -3.0 degrees Celsius and wait for Temperera-ture to reach setpoint
36 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
37 REM Ensure complete cooling
38 Wait for 15.000 minute(s)
39
40 REM Adding mesylchloride
41 Transfer 400ul from REAGENT_2[1](MsCl/DCM) to RB1_1to96[1-72] using Flush Diluter1
42 REM Reacts 30 min @ -3 °C
43 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
44 Wait for 4.000 minute(s)
45 Repeat from step 43, 5 times
46
47 REM Reacts 60 min @ 25 C

95 Pause
96
97 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4
98 REM THF wash 3 times
99 Dispense System Fluid Flush Diluter 2 800ul to RB1_1to96[1-72]
100 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.
101 Go to ChemFile MTY72_3M.CHM, line 1
102 Go to ChemFile MTY72_3M.CHM, line 1
103 Repeat from step 99, 2 times
104
105 REM Alternating MeOH/DCM wash, 2 cycles
106 Dispense System Fluid Flush Diluter 3 800ul to RB1_1to96[1-72]
107 Mix "RB1_1to96" for 3.00 minutes at 300 rpm(s) and wait.
108 Go to ChemFile MTY72_3M.CHM, line 1
109
110 Dispense System Fluid Disdu1_4* 800ul to RB1_1to96[1-72]
111 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.
112 Go to ChemFile MTY72_3M.CHM, line 1
113 Go to ChemFile MTY72_3M.CHM, line 1
114
115 Repeat from step 106, 1 times
116
117 Dispense System Fluid Disdu1_4* 800ul to RB1_1to96[1-72]
118 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.
119 Go to ChemFile MTY72_3M.CHM, line 1
120 Repeat from step 117, 1 times
121
122 REM Washing procedure has ended
123
124 REM Setup for cleavage:
125 REM * Cleavage vials
126 REM * Lower pressure
127 REM * Add 100 mL TFA/DCM 1:1 mixture to Reagent3
128 REM * Add 100 mL CH3CN to Reagent4
129 Pause
130
131 REM Adding cleavage solution, 1hr
132 Transfer 1000ul from REAGENT_3[1](TFA/DCM) to RB1_1to96[1-72] using Flush Diluter1
133 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
134 Wait for 4.000 minute(s)
135 Repeat from step 133, 11 times
136 REM PULSE EMPTY!
137 Go to ChemFile PULSEMP1.CHM, line 1
138
139 REM Washing with CH3CN
140 Transfer 500ul from REAGENT_4[1](CH3CN) to RB1_1to96[1-72] using Flush Diluter1
141 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.

Ex No.	Structure	HPLC-MS (METHOD B) m/z (M+1)	HPLC-MS (METHOD B) R_t (minutes)
828		422	6.10
829		410	4.20
830		410	4.93
831		508	13.30
832		450	7.87
833		448	7.07

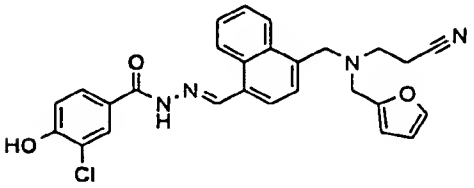
843		468	6.25
844		453	4.87
845		437	2.68
846		436	7.88
847		500	14.12

Ex No.	Structure	HPLC-MS (METHOD A) m/z (M+1)	HPLC-MS (METHOD A) R_t (minutes)
848		484	9.80
849		462	9.38

859		497	10.73
860		474	9.15
861		488	9.55
862		462	9.27
863		470	9.43
864		504	8.98
865		440	8.35
866		454	12.90

^{1}H NMR (DMSO-D6) d 2.37 (m, 8H), 3.44 (s, 2H), 3.90 (s, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 7.4 Hz, 1H), 7.67 (m, 2H), 7.81 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 8.36 (dd, J = 1.7, 7.0 Hz, 1H), 8.83 (d, J = 8.0 Hz, 1H), 9.08 (s, 1H), 10.99 (s, 1H), 11.78 (s, 1H). MS (APCI, pos.): 547.1, 550.1

EXAMPLE 875:



^{1}H NMR (DMSO-D_6) d 2.66 - 2.75 (m, 4H), 3.69 (s, 2H), 4.06 (s, 2H), 6.36 (m, 1H), 6.40 (m, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.51 - 7.66 (m, 4H), 7.77 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.98 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.80 (d, J = 8.5 Hz, 1H), 9.04 (s, 1H), 10.94 (s, 1H), 11.77 (s, 1H). MS (APCI, pos.): 485.1, 487.1

General Procedure for Examples 876 to 877:

The compounds were prepared as single entities according to the following equation

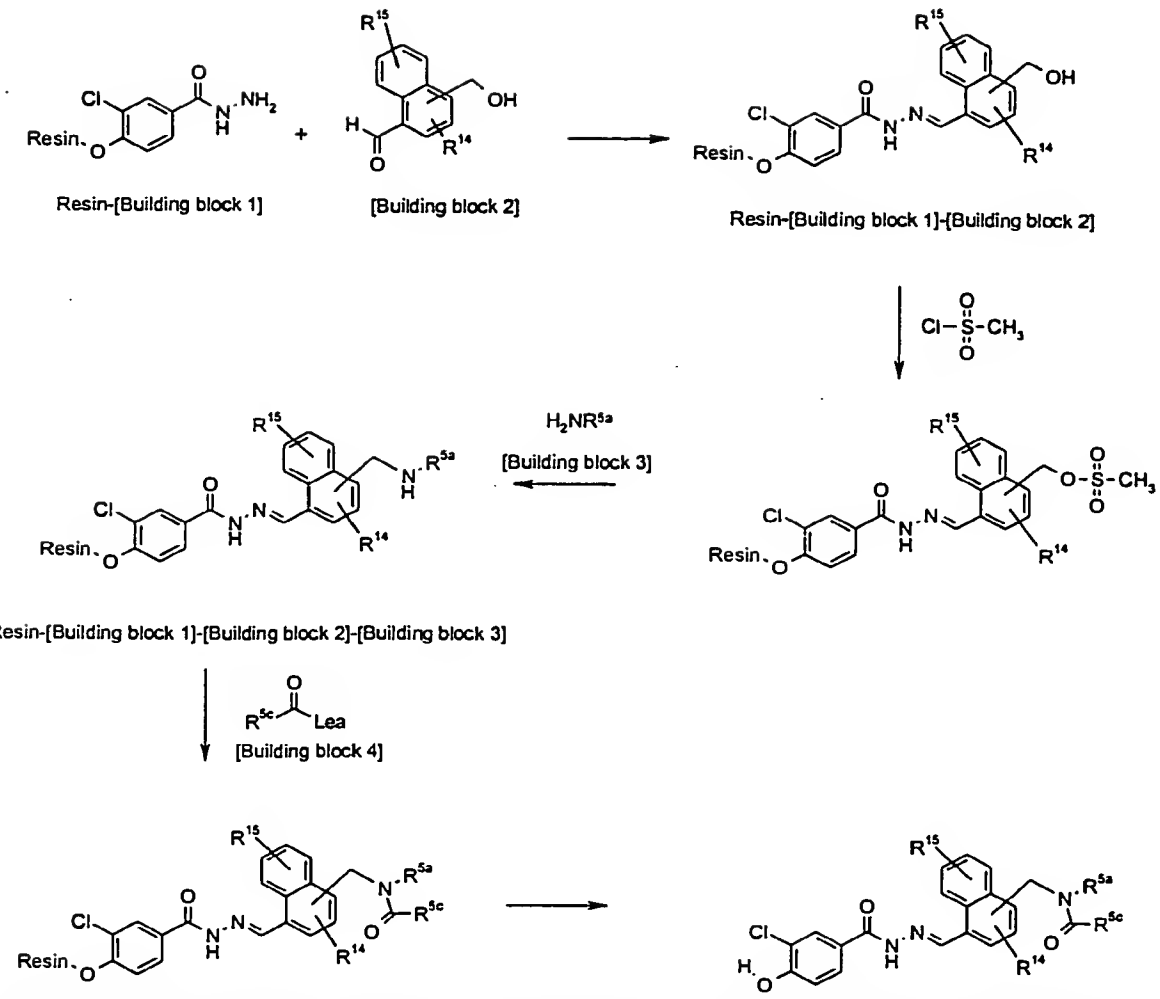
Resin—[Building block 1] ⟶

Resin—[Building block 1]—[Building block 2] ⟶

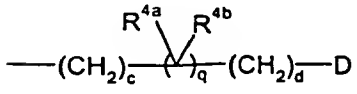
Resin—[Building block 1]—[Building block 2]——[Building block 3] ⟶

Resin—[Building block 1]—[Building block 2]——[Building block 3]——[Building block 4]

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid in dichloromethane to give the desired compounds as individual entities according to the following formula



wherein R^{5a}, R^{14}, R^{15} are as defined for formula I and R^{5c} is

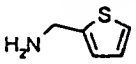
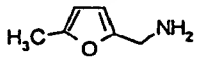
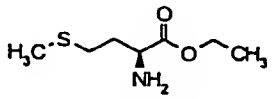
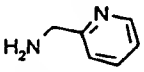
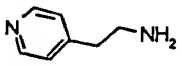
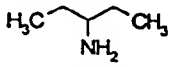
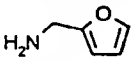
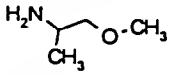
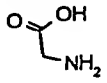
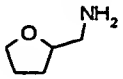
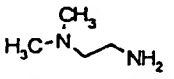
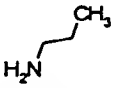
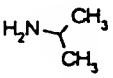
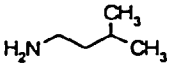
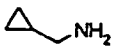
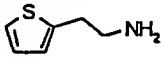
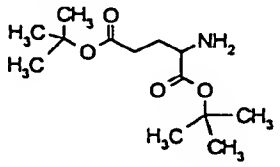
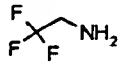
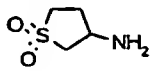


where R^{4a}, R^{4b}, c, q, d, and D are as defined for formula I or

-D' where -D' is defined as a subset of -D that contains an activated carboxylic acid capable of reacting as an electrophile and

Lea is a leaving group such as chloro, bromo, iodo, carboxylate,

[Building block 3]:

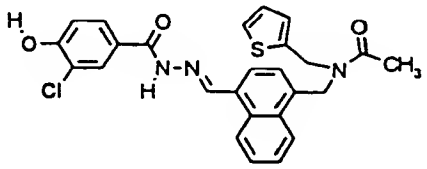
2-Thiophenemethylamine 	5-Methyl-2-furanmethylamine 	L-Methionine ethyl ester 
2-(Aminomethyl)pyridine 	4-(2-Aminoethyl)pyridine 	3-Aminopentane 
Furfurylamine 	2-Methoxyisopropylamine 	Cyclopropylamine 
Glycine 	2-Furanylmethylamine 	N,N-Dimethylethylenediamine 
Ethylamine 	Methylamine 	Propylamine 
Isopropylamine 	Isopentylamine 	Cyclopentylamine 
Cyclopropylmethylamine 	Cyclobutylamine 	Thiophene-2-ethylamine 
Glutamic Acid di tert butylester 	2,2,2-Trifluoroethylamine 	Tetrahydro-3-thiophenamine 1,1-dioxide 

and diisopropylethylamine (100 µL). The mixture was shaken at 25 °C for 16 hours. The solvent was removed by suction and the resin was washed with DMSO (2 x 0.5 mL) andTHF (3 x 0.5 mL). To a solution of N-*tert*- butoxycarbonyl-proline (46 mg, 0.21 mmol) in THF (0.5 mL) was added diisopropylcarbodiimide (16 µL, 0.2 mmol). This solution was allowed to react at 25 °C for 10 minutes and then added to the resin. The suspension was shaken at 25 °C for 16 hours after which the resin was isolated by suction and washed with THF (3 x 0.5 mL), DMF (3 x 0.5 mL) THF (3 x 0.5 mL), CH_3OH (0.5 mL), CH_2Cl_2 (0.5 mL), CH_3OH (0.5 mL), CH_2Cl_2 (4 x 0.5 mL). The compound was cleaved from the resin by shaking for 1 hour at 25 °C with a 50% solution of trifluoroacetic acid in CH_2Cl_2 (1 mL). The mixture was filtered and the resin was extracted with acetonitrile (1 mL). The combined extracts were concentrated in vacuo. The residue was redissolved in a mixture of CH_3OH (0.5 mL) and acetonitrile (0.5 mL) and concentrated in vacuo to give the title compound.

HPLC-MS (METHOD B): R_t = 3.90 min; m/z = 507 (M+1).

EXAMPLE 877:

3-Chloro-4-hydroxybenzoic acid ((4-(4-trifluoromethoxybenzylamino)methyl)naphthylmethylene)hydrazide



Resin bound 3-chloro-4-hydroxybenzoic acid (4-hydroxymethylnaphthylmethylene)hydrazide (resin-[building block 1]-[building block 2]) (50 mg) was swelled in a 1:1 mixture of CH_2Cl_2 and N-methyl-2-pyrrolidone (0.5 mL) for 15 minutes and then washed with CH_2Cl_2 (3 x 0.5 mL). 800 µL of a 1:1 mixture of CH_2Cl_2 and diisopropylethylamine was added to the resin which subsequently was cooled to -3 °C. A solution of 100 µL methanesulfonylchloride dissolved in 300 µL was added and allowed to react at -3 °C for 30 minutes then at 25 °C for 1 hour. Filtration of the resin was followed by washing with CH_2Cl_2 (2 x 1 mL) and N-methyl-2-pyrrolidone (2 x 0.5 mL). 600 µL of a solution of 4-trifluoromethoxybenzylamine (45.8 mg, 0.24 mmol, 0.4M) and KI (10 mg, 0.06 mmol, 0.1M) in N-methyl-2-pyrrolidone (0.5 mL) and

5 REM Dipense resin bound benzylic alchohol to wells
6
7
8 REM Setup Diluter1=DCM, D2=NMP (N-methyl-2-pyrrolidone), D3=NMP, D4=DCM
9 REM Adjust pressure
10 REM Add 100 mL DIEA/DCM 1:1 mixture to Reagent1
11 REM Add 70 mL MsCl/DCM 1:3 mixture to Reagent2
12 REM Add 100 mL TFA/DCM 1:1 mixture to Reagent3
13 REM Add 100 mL CH3CN to Reagent4
14 REM Nitrogen for cooling
15
16 Pause
17 REM Initialising...
18
19 REM Subroutine Empty1_72_3min is called twice to remove DCM/NMP from dispensed resin
20 Go to ChemFile MTY72_3M.CHM, line 1
21 Go to ChemFile MTY72_3M.CHM, line 1
22
23 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and with Flush Diluter 4
24
25 REM Washing with DCM, 3 times
26 Dispense System Fluid Disdu1_4* 500ul to RB1_1to96[1-72]
27 Mix "RB1_1to96" for 3.00 minutes at 300 rpm(s) and wait.
28 REM Subroutine Empty1_72_3min
29 Go to ChemFile MTY72_3M.CHM, line 1
30 Repeat from step 26, 2 times
31
32 REM Adding DCM/DIEA mixture from Reagent1
33 Transfer 800ul from REAGENT_1[1](DCM/DIEA) to RB1_1to96[1-72] using Flush Diluter1
34 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
35 Set Temperature of rack "RB1_1to96" to -3.0 degrees Celsius and wait for Temperature to reach setpoint
36 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
37 REM Ensure complete cooling
38 Wait for 15.000 minute(s)
39
40 REM Adding mesylchloride
41 Transfer 400ul from REAGENT_2[1](MsCl/DCM) to RB1_1to96[1-72] using Flush Diluter1
42 REM Reacts 30 min @ -3 °C
43 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.
44 Wait for 4.000 minute(s)
45 Repeat from step 43, 5 times
46
47 REM Reacts 60 min @ 25 C
48 Set Temperature of rack "RB1_1to96" to 25.0 degrees Celsius and wait for Temperature to reach setpoint
49 Mix "RB1_1to96" for 1.00 minutes at 300 rpm(s) and wait.

97 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4
98 REM THF wash 3 times
99 Dispense System Fluid Flush Diluter 2 500ul to RB1_1to96[1-72]
100 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.
101 Go to ChemFile MTY72_3M.CHM, line 1
102 Go to ChemFile MTY72_3M.CHM, line 1
103 Repeat from step 99, 2 times
104 Go to ChemFile Acylation.CHM, line 1
105 Go to ChemFile WASH.CHM, line 1
106 Go to ChemFile Cleavage.CHM, line 1
107 REM The End

The following chemfile is called to acylate the amines:

ChemFile C:\ACT_1328\Acetyl.CHM

1 REM Acetylation procedure
2 REM Charge REAGENT_5 with 100 mL Acetic anhydride/THF 1:4 v/v
3 REM * Diluter2: THF
4 REM Addition of acylation reagent
5 Dispense Sequence C:\R3-A.DSP with 600 µL to RB1to96 rack using Flush Diluter 2
6 Mix for 1.00 minutes at 300 rpm(s)
7 Wait for 5.000 minute(s)
8 Repeat from step 6, 60 times
9 Go to ChemFile MTY72_3M.CHM, line 1
10 Go to ChemFile MTY72_3M.CHM, line 1
11 Return

The following chemfile is called to wash the resin bound products:

ChemFile C:\ACT_1328\WASH.CHM

1 REM Washing procedure
2 REM Systemfluids:
3
4 REM * Diluter2: THF
5 REM * Diluter3: MeOH
6
7 Flush Arm1 with Flush Diluter1 and Flush Diluter 2 , Arm2 with Flush Diluter 3 and Flush Diluter 4
8 REM THF wash 3 times
9 Dispense System Fluid Flush Diluter 2 800ul to RB1_1to96[1-72]
10 Mix "RB1_1to96" for 10.00 minutes at 300 rpm(s) and wait.

19 REM PULSE EMPTY!
20 Go to ChemFile PULSEMP1.CHM, line 1
21 Return

The following chemfile is called to empty the wells of the reaction block.:

ChemFile C:\ACT_1328\MTY72_3M.CHM Page 1

1 REM Subroutine Empty1_72_3min
2 Empty RB1_1to96 for 5.000 minute(s)
3 Return

The following chemfile is called to empty the wells of the reaction block into the cleavage vials containing the final product in a controlled manner.

ChemFile C:\ACT_1328\PULSEMP1.CHM Page 1

1 Empty RB1_1to96 for 1 second(s)
2 Wait for 4 second(s)
3 Repeat from step 1, 11 times
4 Empty RB1_1to96 for 5.000 minute(s)
5 Return

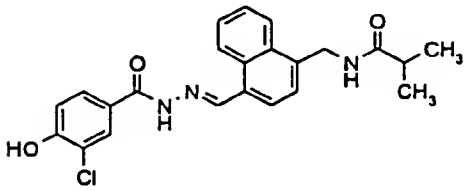
Dispense sequence C:\ACT_1328\R2-A.DSP is a subroutines that control the combinatorial addition of the amines into the reaction block in the syntheziser.

Dispense sequence C:\ACT_1328\R3-A.DSP is a subroutines that control the combinatorial addition of the acylating agents into reaction block in the syntheziser.

Examples of compounds from this library were characterised by HPLC-MS (molecular mass & retention time) including the following examples 878 to 881.

EXAMPLE 882:

N-{4-[3-chloro-4-hydroxybenzoyl)-hydrazonemethyl]-1-naphthyl}methyl *iso*-propyl amide



Preparation of *N*-4-Formylnaphthylmethyl isopropyl amide:

A mixture of 4-bromomethyl-1-naphthaldehyde ethyleneacetal (447 mg, 1.52 mmol) and NaN_3 (221 mg, 3.4 mmol) in 10 mL DMF was warmed up to 100 °C and stirred for 30 min. Solution turned orange. The reaction was filtered and the clear solution was concentrated to 391 mg of yellow oil. This oil (249 mg) together with triphenylphosphine (260 mg, 0.99 mmol) was dissolved in 10 mL of THF. The reaction mixture was left overnight followed by the addition of water. Ninhydrin test revealed the formation of an amine. This amine was extracted into ethyl acetate layer, dried to give an oil. This oil was dissolved in CH_2Cl_2, EDC, DMAP and 2-methylpropionic acid were added. The reaction mixture was left for 2 days. Column chromatography eluted with ethyl acetate afforded the amide. Deprotection of di-ethyleneacetal was achieved by 10% HCl in THF to give the title compound (50 mg).

^{1}H NMR ($CDCl_3$): d 1.2 (d, 6H), 2.4 (m, 1H), 4.9 (d, 2H), 6.1 (b, 1H), 7.5 (d, 1H), 7.6 (m, 2H), 7.8 (d, 1H), 8.0 (d, 1H), 9.2 (d, 1H), 10.3 (s, 1H).

The title compound was prepared similarly as described above.

^{1}H NMR (DMSO-D_6): d 1.0 (d, 6H), 2.4 (m, 1H), 4.7 (s, 2H), 7.0 (d, 1H), 7.4 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 7.8 (d, 1H), 7.9 (s, 1H), 8.1 (d, 1H), 8.3 (s, 1H), 8.8 (d, 1H), 9.0 (s, 1H), 10.9 (s, 1H), 11.7 (s, 1H); ms (APCI negative); 422.

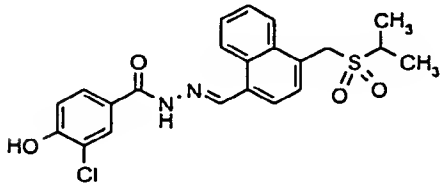
EXAMPLE 883:

4-[3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthylmethyl iso-propylsulfoxide

^{1}H NMR (DMSO-D_6): d 1.3 (dd, 6H), 3.0 (m, 1H), 4.3 (d, 1H), 4.7 (d, 1H), 7.1 (d, 1H), 7.6 (m, 3H), 7.8 (d, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 8.2 (d, 1H), 8.8 (d, 1H), 9.1 (s, 1H), 11.0 (s, 1H), 11.8 (s, 1H); ms (APCI negative); 427, 337.

EXAMPLE 884:

4-[3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthylmethyl iso-propylsulfone

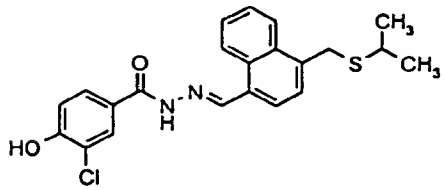


Similarly, the title compound was prepared.

^{1}H NMR (DMSO-D_6): d 1.3 (d, 6H), 3.4 (m, 1H), 5.0 (s, 2H), 7.0 (d, 1H), 7.6 (m, 3H), 7.7 (d, 1H), 7.9 (d, 2H), 8.2 (d, 1H), 8.7 (d, 1H), 9.0 (s, 1H), 10.9 (s, 1H), 11.8 (s, 1H); ms (APCI negative); 443, 336.

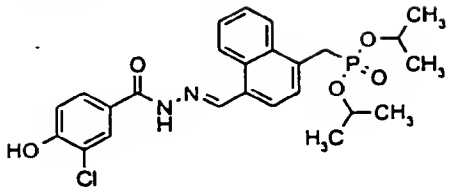
EXAMPLE 885:

4-[3-chloro-4-hydroxybenzoyl)-hydrazonomethyl]-1-naphthylmethyl iso-propylsulfide

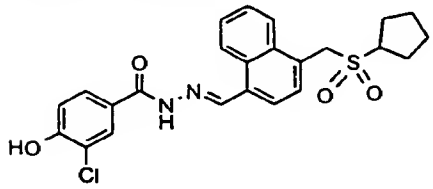


Similarly, the title compound was prepared.

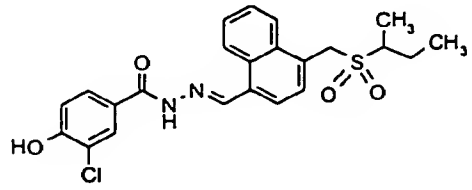
EXAMPLE 890:



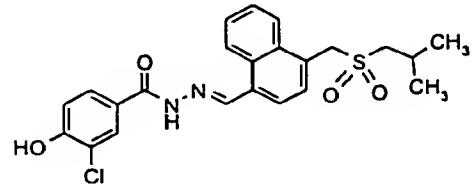
EXAMPLE 891:



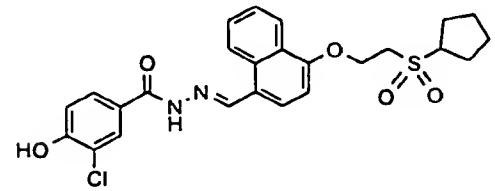
EXAMPLE 892:



EXAMPLE 893:

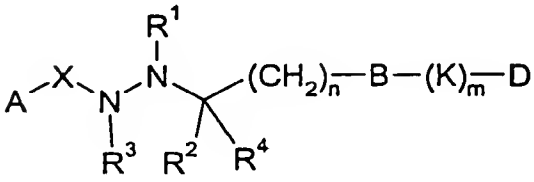


EXAMPLE 894:



Claims

1. A compound of the general formula I:



(I)

wherein:

R^1 and R^2 independently are hydrogen or lower alkyl or together form a valence bond;

R^3 and R^4 independently are hydrogen or lower alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

X is >C=O, >C=S, >C=NR^5 or >SO_2;

wherein R^5 is hydrogen, lower alkyl, aryl-lower alkyl or -OR^6;

wherein R^6 is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

A is

R^7 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SO_2NR^{11}R^{12}$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-OCH_2CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$ or $-OSO_2CF_3$;

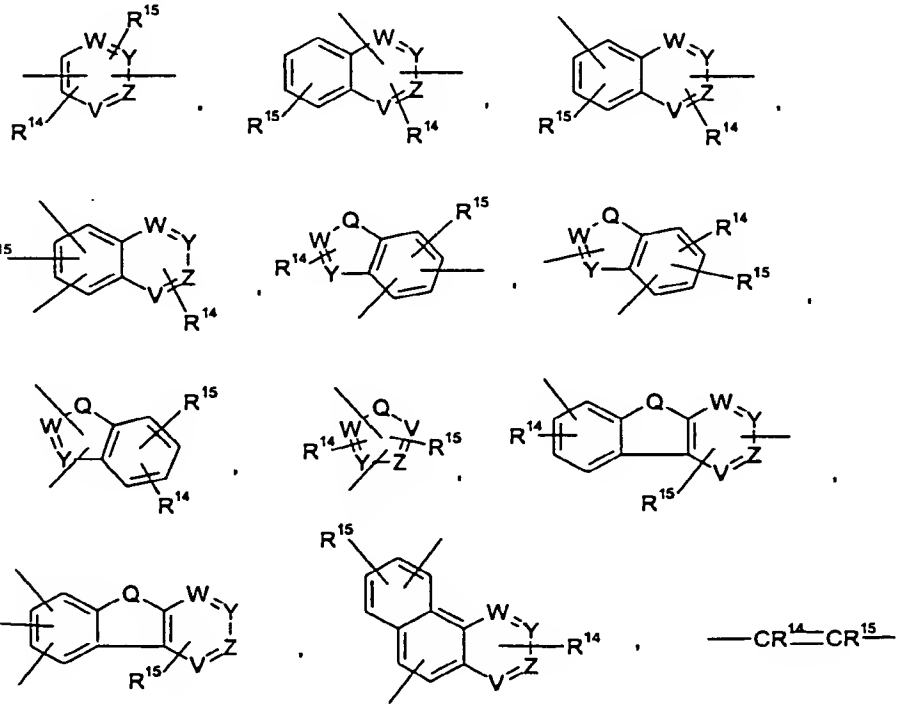
R^8 and R^9 independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, lower alkyl, aryl, $-SCF_3$, $-SR^{11}$, $-CHF_2$, $-OCHF_2$, $-OSO_2R^{11}$, $-CONR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2NR^{11}R^{12}$, $-OCOR^{11}$, $-CO_2R^{13}$ or $-OSO_2CF_3$, or R^8 and R^9 together form a bridge $-OCH_2O-$ or $-OCH_2CH_2O-$;

wherein R^{11} and R^{12} independently are hydrogen, $-COR^{13}$, $-SO_2R^{13}$, lower alkyl or aryl;

wherein R^{13} is hydrogen, lower alkyl, aryl-lower alkyl or aryl; and

R^{10} is hydrogen, lower alkyl, aryl-lower alkyl or aryl;

B is



or a valence bond;

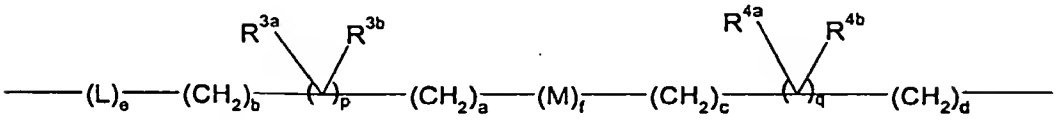
wherein:

wherein R^{24} and R^{25} independently are hydrogen, $-COR^{26}$, $-SO_2R^{26}$, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{26} is hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

R^{23} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

K is



wherein:

R^{3a}, R^{3b}, R^{4a} and R^{4b} independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-NO_2$, $-OR^{24a}$, $-NR^{24a}R^{25a}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SR^{24a}$, $-CHF_2$, $-OCHF_2$, $-OCF_2CHF_2$, $-OSO_2CF_3$, $-CONR^{24a}R^{25a}$, $-CH_2CONR^{24a}R^{25a}$, $-OCH_2CONR^{24a}R^{25a}$, $-CH_2OR^{24a}$, $-CH_2NR^{24a}R^{25a}$, $-OCOR^{24a}$ or $-CO_2R^{24a}$;

wherein R^{24a} and R^{25a} independently are hydrogen, $-COR^{26a}$, $-SO_2R^{26a}$, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{26a} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

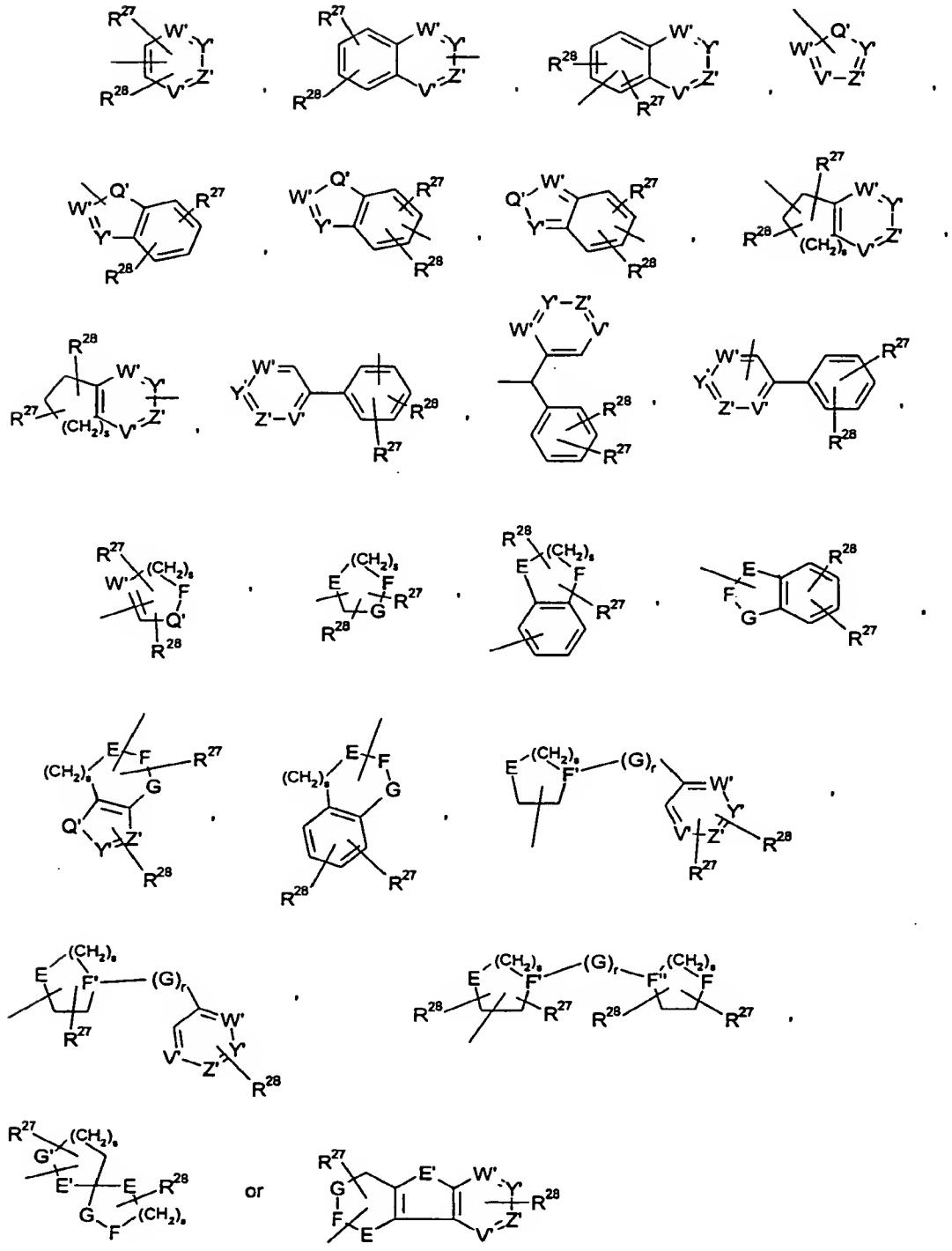
or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, or R^{3a} and R^{4b} together form a bridge $-(CH_2)_i-$;

wherein i is 1, 2, 3 or 4;

a, b, c and d independently are 0, 1, 2, 3 or 4;

e, f and p independently are 0 or 1;



wherein:

r is 0 or 1;

R^{36} and R^{39} independently are hydrogen, lower alkyl, aryl or aryl-lower alkyl; and

R^{38} is hydrogen, $-OR^{40}$, $-NR^{40}R^{41}$, lower alkyl, aryl, aryl-lower alkyl, $-SCF_3$, $-SR^{40}$, $-CHF_2$, $-OCHF_2$, $-OCF_2CHF_2$, $-CONR^{40}R^{41}$, $-(CH_2)_xCONR^{40}R^{41}$, $-O(CH_2)_xCONR^{40}R^{41}$, $-(CH_2)_xOR^{40}$, $-(CH_2)_xNR^{40}R^{41}$, $-OCOR^{40}$ or $-CO_2R^{40}$;

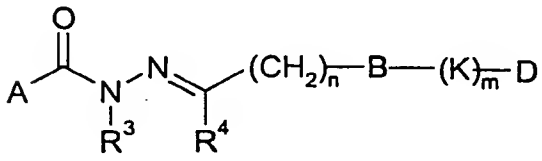
wherein x is 1, 2, 3 or 4;

R^{40} and R^{41} independently are hydrogen, $-COR^{42}$, $-SO_2R^{42}$, lower alkyl, aryl or aryl-lower alkyl;

wherein R^{42} is hydrogen, lower alkyl, aryl or aryl-lower alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

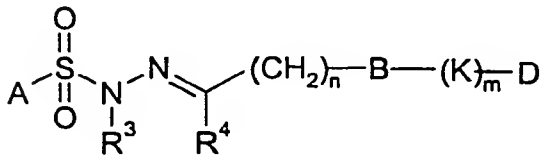
2. A compound according to claim 1 having the following formula II:



(II)

wherein A, B, K, D, R^3, R^4, n and m are as defined in claim 1.

3. A compound according to claim 1 having the following formula III:



(III)

wherein A, B, K, D, R^3, R^4, n and m are as defined in claim 1.

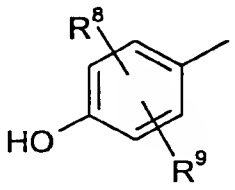
wherein R^7, R^8 and R^9 are as defined in claim 1.

9. A compound according to claim 7 or 8, wherein R^7 is halogen, lower alkyl, -OH, $-NO_2$, -CN, $-CO_2H$, -O-lower alkyl, aryl, aryl-lower alkyl, $-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ or $-OCF_3$.

10. A compound according to any one of the claims 7 to 9, wherein R^8 and R^9 independently are hydrogen, halogen, -OH, $-NO_2$, $-NH_2$, -CN, $-OCF_3$, $-SCF_3$, $-CF_3$, $-OCH_2CF_3$, -O-lower alkyl, lower alkyl or phenyl and R^{10} is hydrogen, lower alkyl or phenyl.

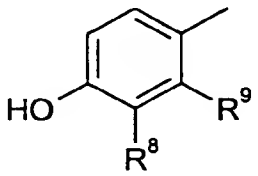
11. A compound according to claim 10, wherein R^8 and R^9 independently are hydrogen, halogen, -O-lower alkyl, $-NH_2$, -CN or $-NO_2$ and R^{10} is hydrogen.

12. A compound according to claim 8, wherein A is



wherein R^8 and R^9 independently are as defined in any one of the claims 10 or 11.

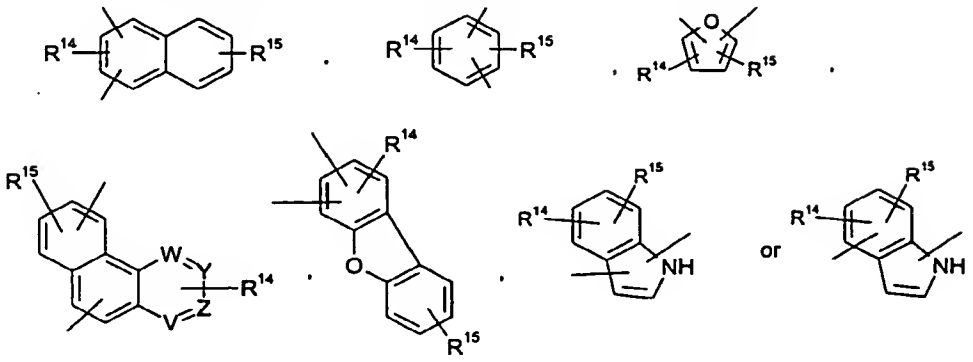
13. A compound according to claim 12, wherein A is



wherein R^8 is hydrogen, halogen, -O-lower alkyl, $-NH_2$, -CN or $-NO_2$; and R^9 is hydrogen or halogen.

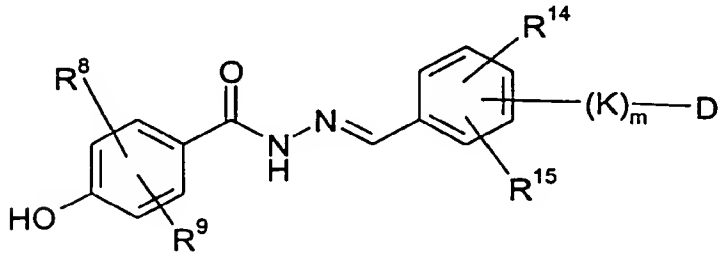
14. A compound according to any one of the claims 7 to 13 having the following formula V:

17. A compound according to claim 15, wherein B is



wherein R^{14} and R^{15} are as defined in claim 15, and V, W, Z and Y are as defined in claim 1.

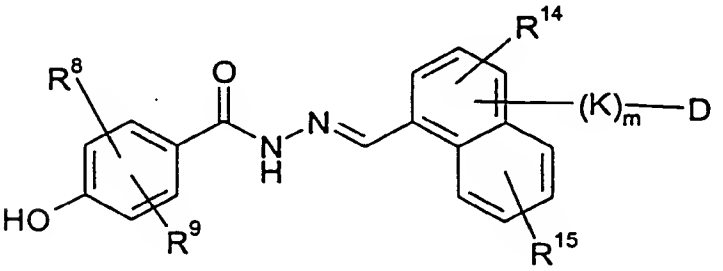
18. A compound according to claim 17 having the following formula VI:



(VI)

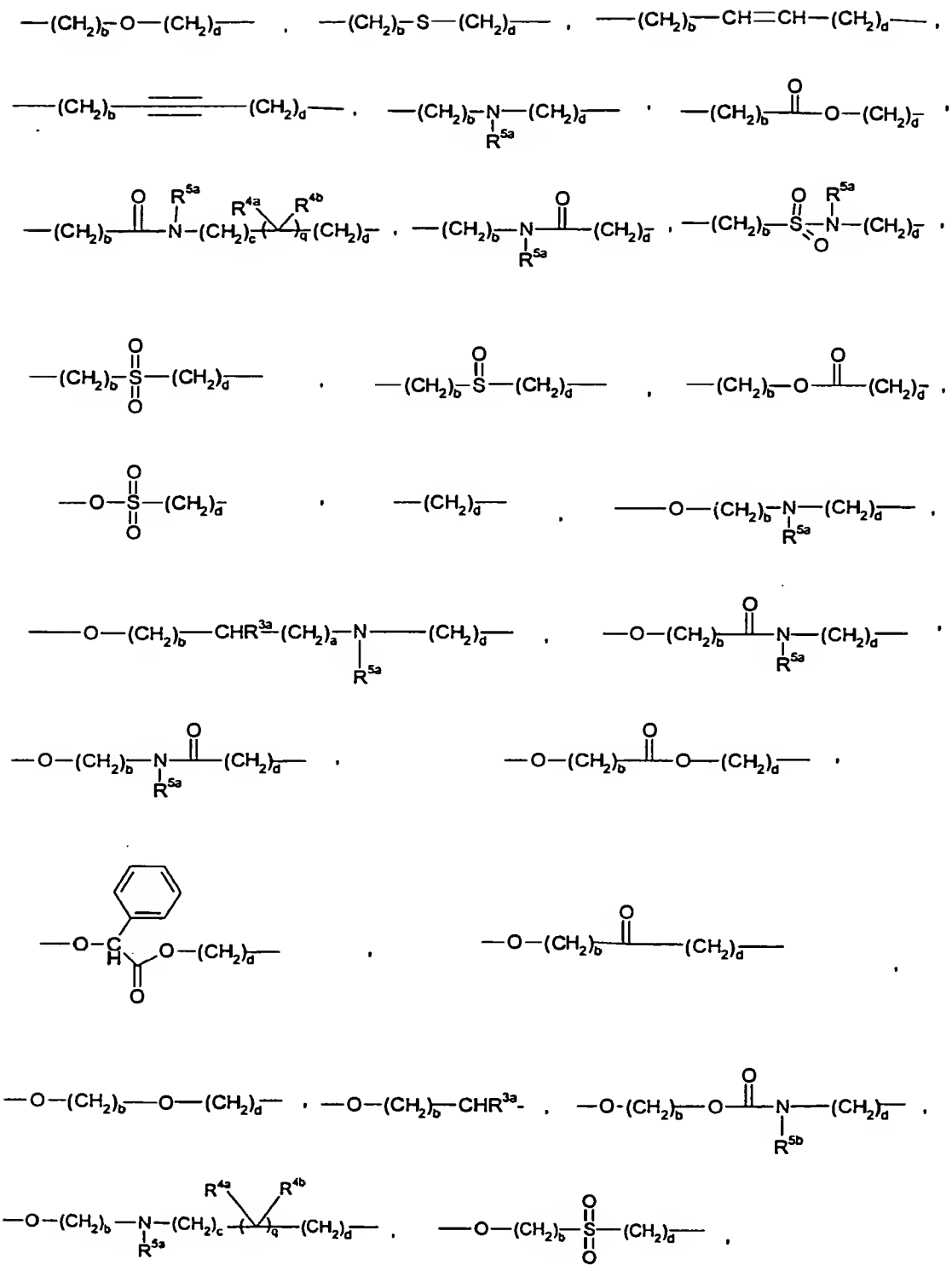
wherein R^{14} and R^{15} are as defined in claim 15, R^8 and R^9 are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

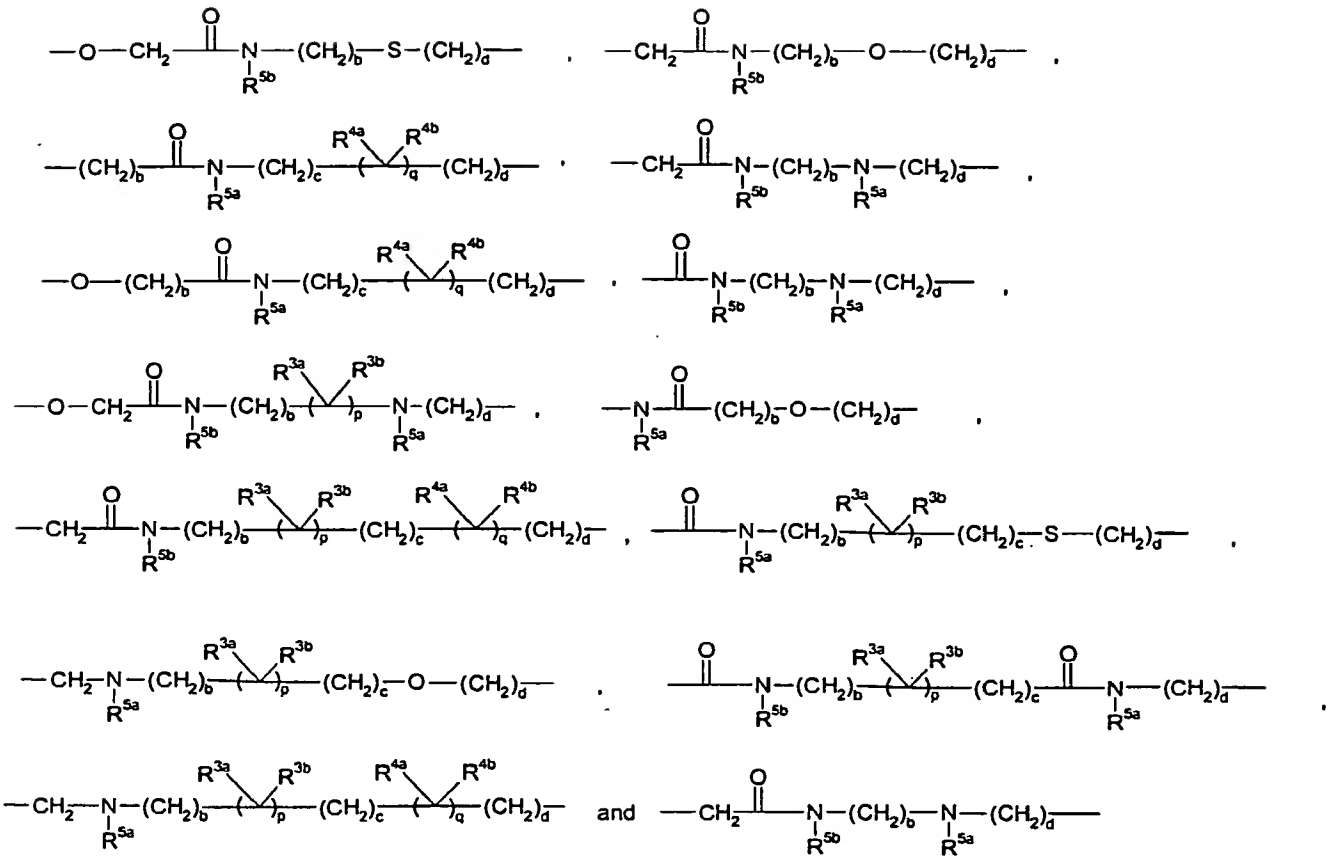
19. A compound according to claim 17 having the following formula VII:



(VII)

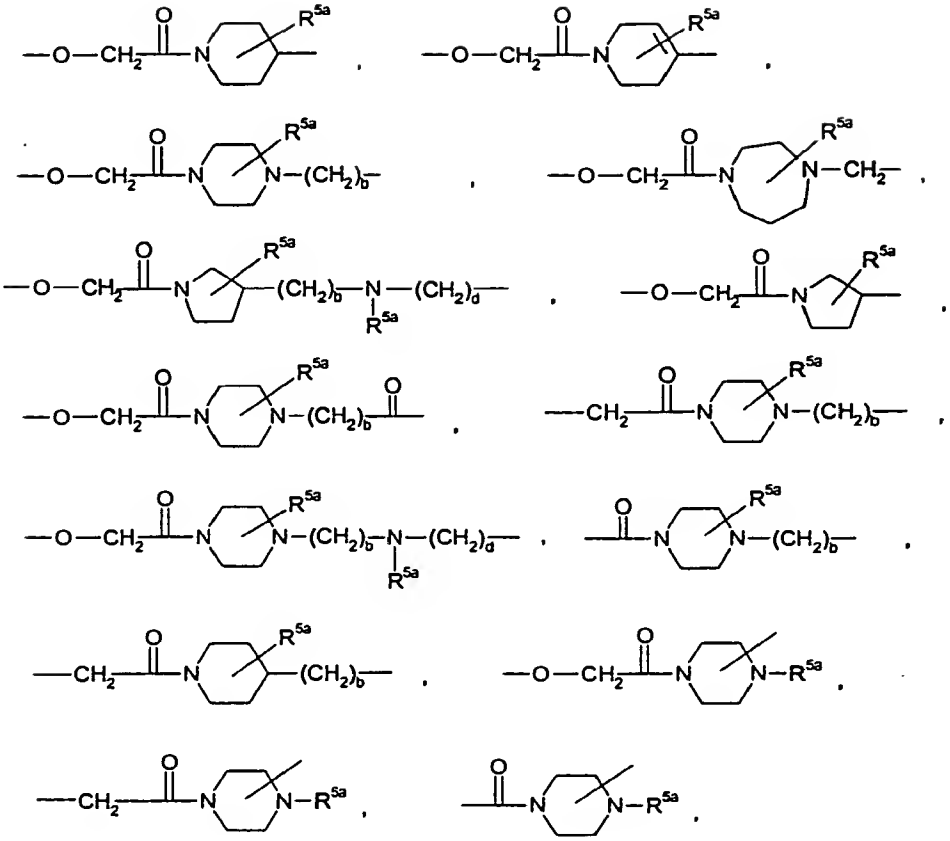
wherein R^{14} and R^{15} are as defined in claim 15, R^8 and R^9 are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

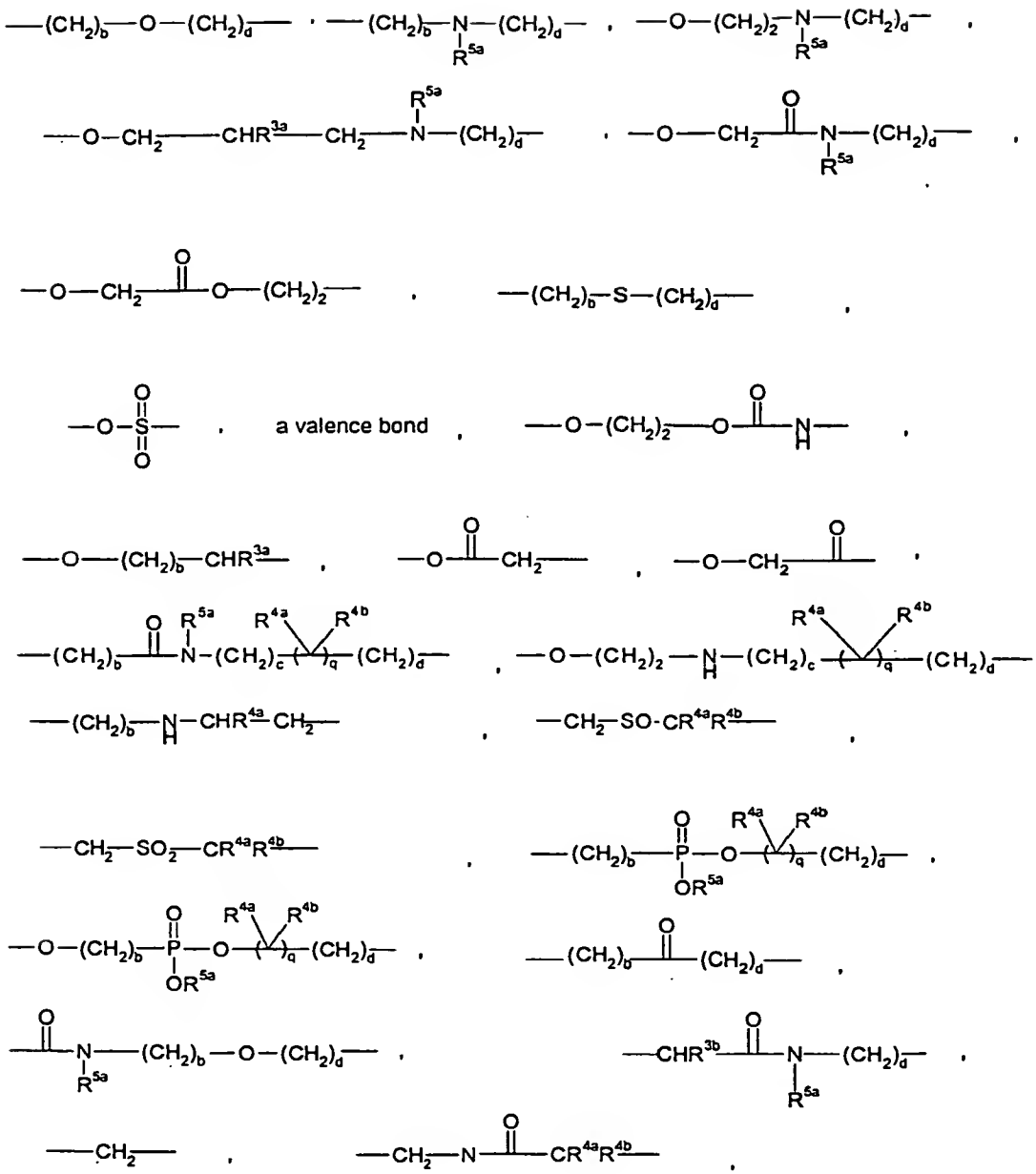


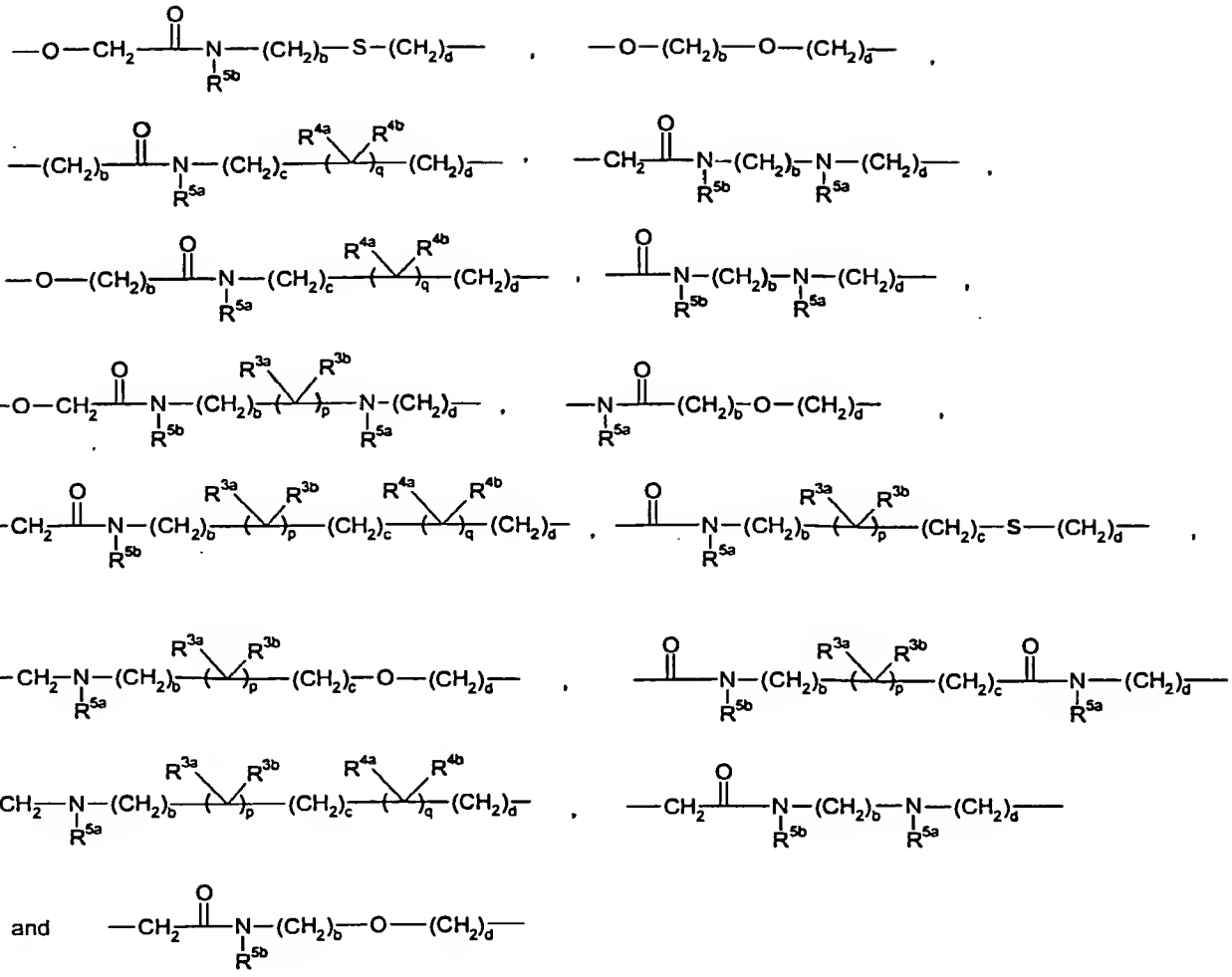


wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, a, b, c, d, p and q are as defined in claim 1.

23. A compound according to claim 22, wherein K is selected from the group consisting of




a valence bond

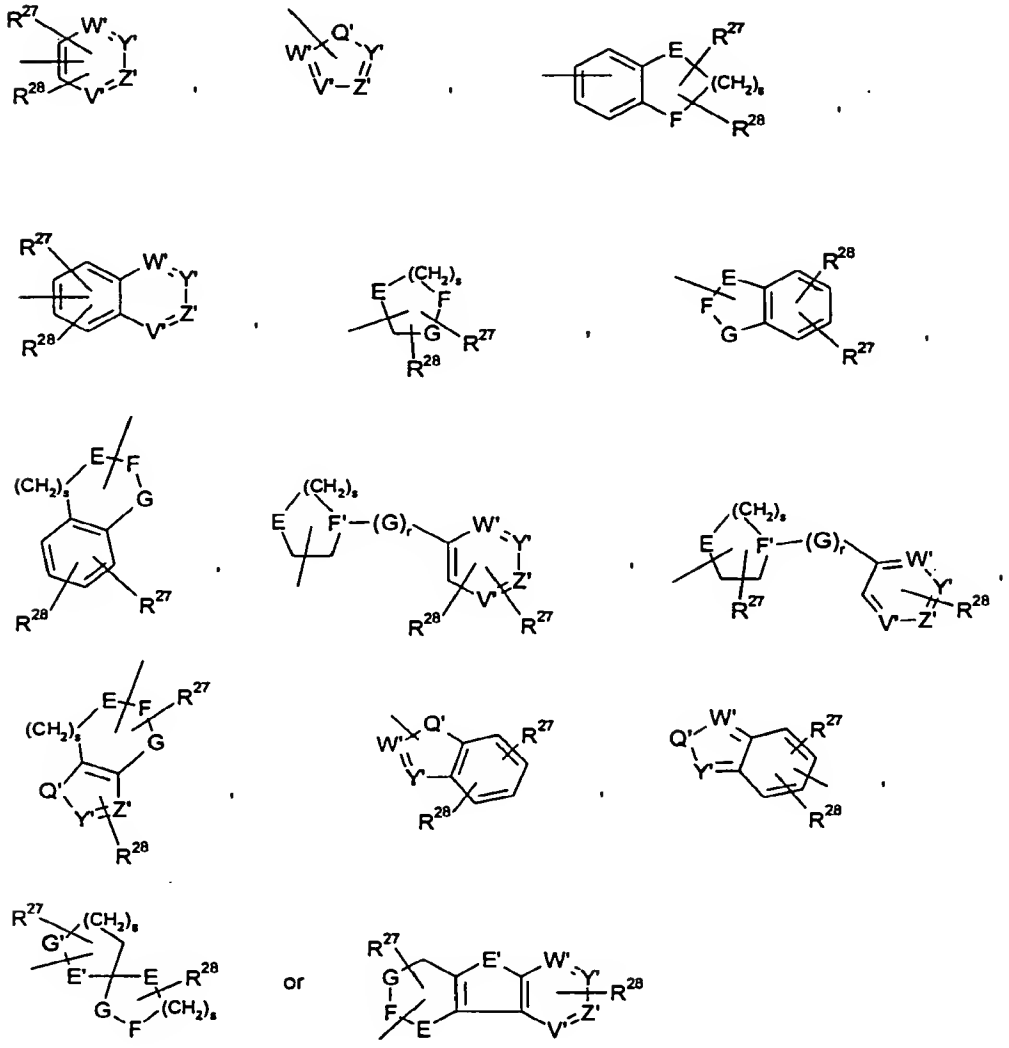


wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, b, c, d, p and q are as defined in claim 1.

25. A compound according to any one of the claims 22 to 24, wherein R^{5a} and R^{5b} independently are hydrogen, lower alkyl, -OH, $-(CH_2)_kOR^{6a}$, aryl, aryl-lower alkyl, $-CH_2CF_3$, $-(CH_2)_g-COOR^{43}$, $-COOR^{43}$, $-(CH_2)_k-CN$ or $-(CH_2)_k-NR^{6a}R^{6b}$ wherein g, k, R^{43}, R^{6a} and R^{6b} are as defined in claim 1.

26. A compound according to claim 25, wherein g and k independently are 1, 2 or 3, R^{6a} and R^{6b} independently are hydrogen, lower alkyl such as methyl or ethyl, or aryl such as phenyl,

30. A compound according to claim 29, wherein D is hydrogen,



wherein s, r, R^{27}, R^{28}, V', Y', Z', Q', Z', W', E, E', F, F', G and G' are as defined in claim 1.

31. A compound according to claim 29, wherein D is hydrogen,

such as methyl, isopropyl or tert-butyl; lower alkylthio; $-SCF_3$; $-CH_2OH$; -COO-lower alkyl or $-CONH_2$; and R^{39} is hydrogen, lower alkyl, aryl or aryl-lower alkyl.

33. A compound according to any one of the claims 1 to 32 for use as a medicament.

34. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 32 together with one or more pharmaceutically acceptable carriers or excipients.

35. A pharmaceutical composition according to claim 34 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 1 to 32.

36 A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 32.

37 A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 32.

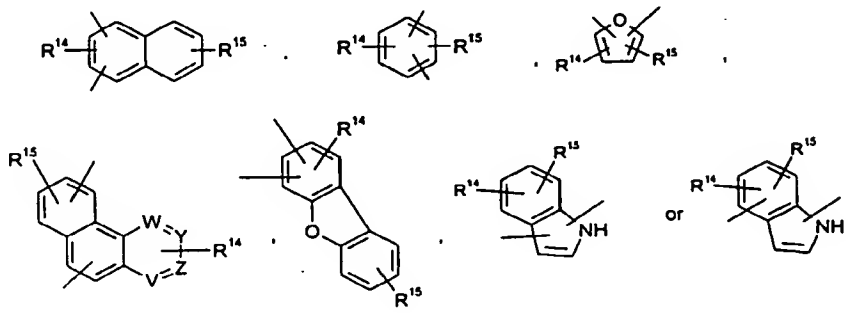
38. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 1 to 32.

39. The method according to any one of the claims 36 to 38 comprising administering to a subject in need thereof an amount of the compound as defined in claim 1 to 33 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

40. Use of a compound according to any one of the claims 1 to 32 for the manufacture of a medicament for treating type I or type II diabetes.

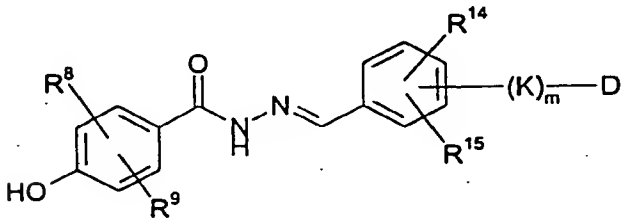
AMENDED CLAIMS
[received by the International Bureau on 01 December 1998 (01.12.98);
original claims 19-43 replaced by new claims 19-47;
remaining claims unchanged (18 pages)]

17. A compound according to claim 15, wherein B is



wherein R^{14} and R^{15} are as defined in claim 15, and V, W, Z and Y are as defined in claim 1.

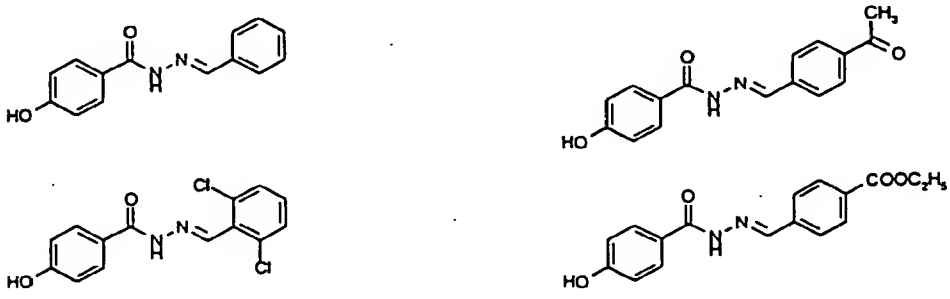
18. A compound according to claim 17 having the following formula VI:



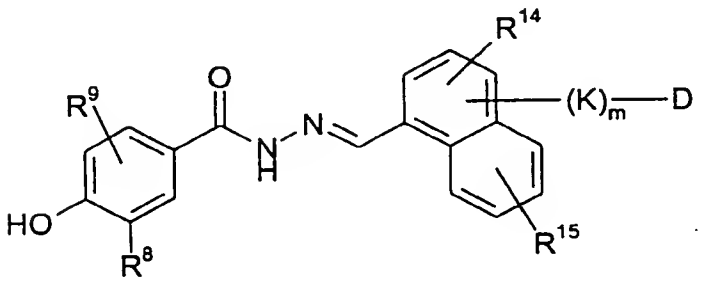
(VI)

wherein R^{14} and R^{15} are as defined in claim 15, R^8 and R^9 are as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

19. A compound according to claim 18 except for the following compounds:



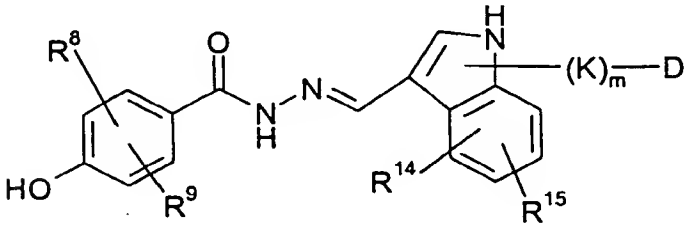
22. A compound according to claim 21 of the formula VIIa:



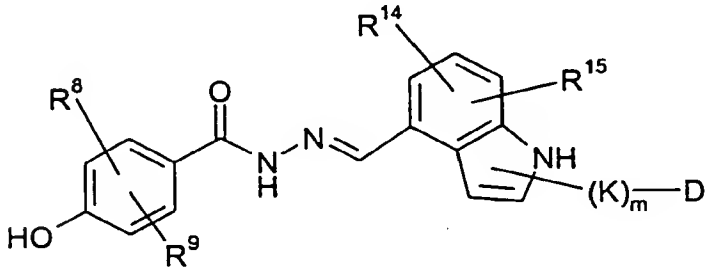
(VIIa)

wherein R^{14} and R^{15} are as defined in claim 15, R^8 is halogen, R^9 is as defined in any one of the claims 1, 10, 11 or 13, and K, D and m are as defined in claim 1.

23. A compound according to claim 17 having the following formulae VIIIa or VIIIb:



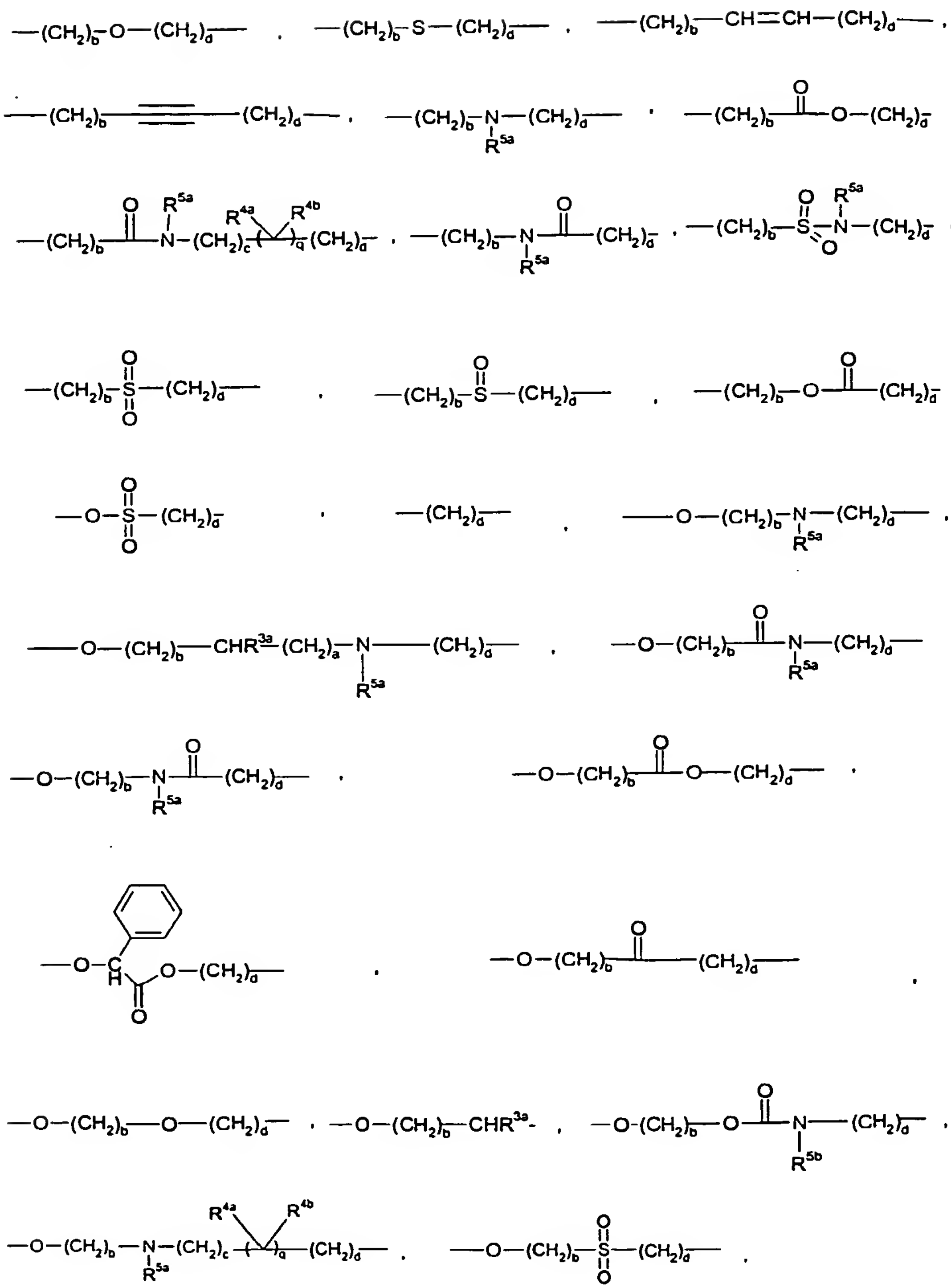
(VIIIa) or

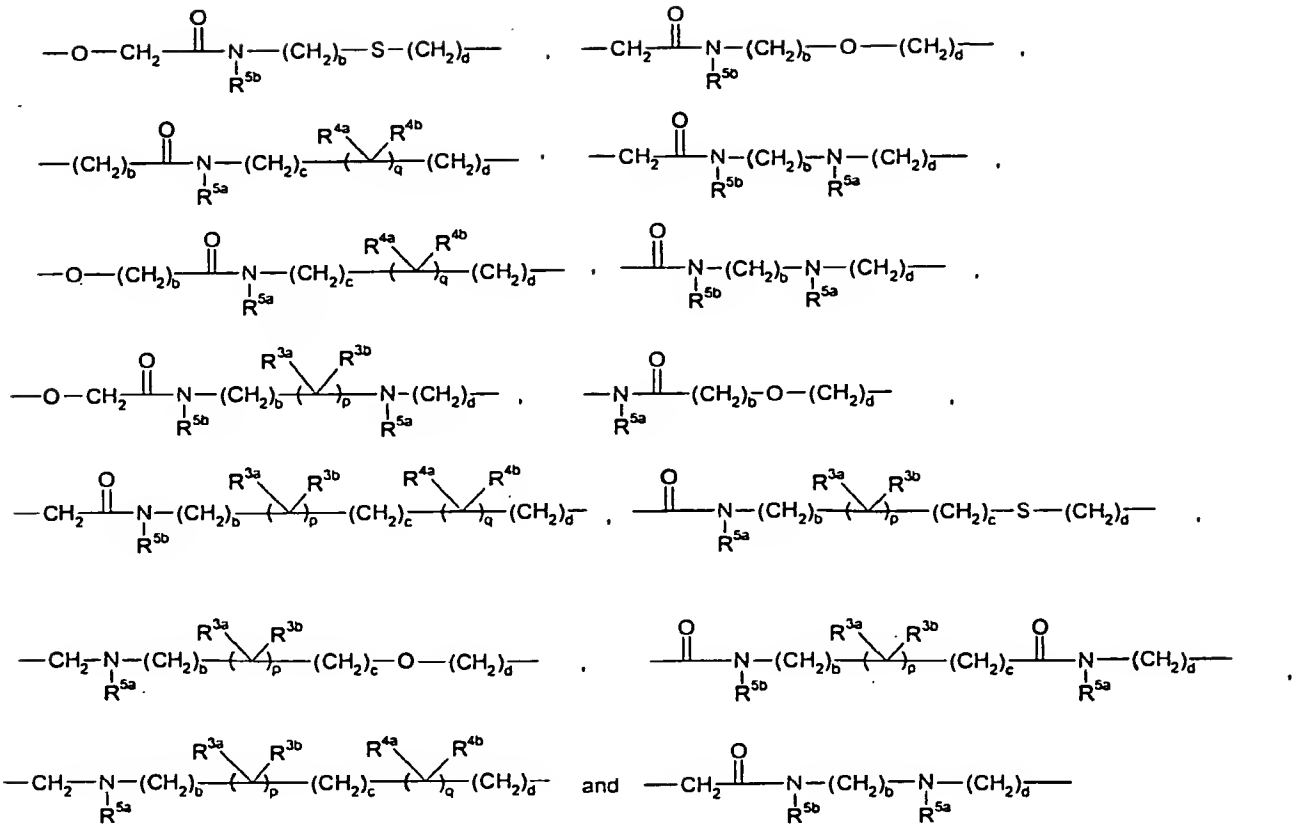


(VIIIb)

wherein R^{14} and R^{15} are as defined in claim 15, R^8 and R^9 are as defined in any one of the claims 1,10, 11 or 13, and K, D and m are as defined in claim 1.

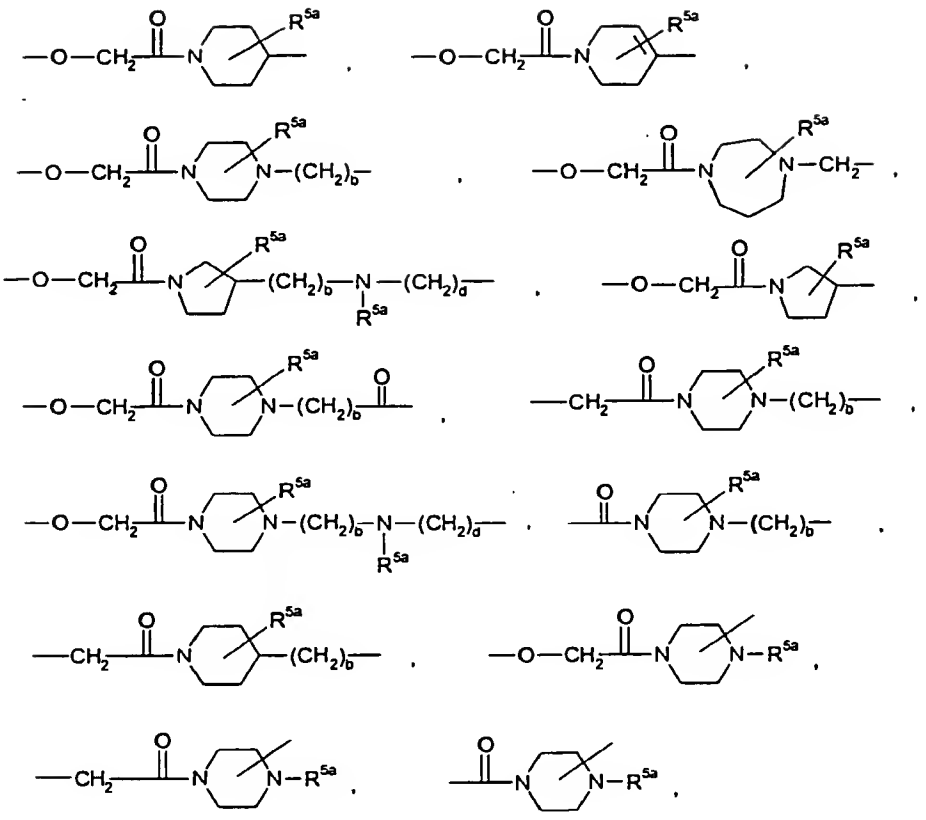
24. A compound according to claim 17 having the following formulae VIIIa' or VIIIb':

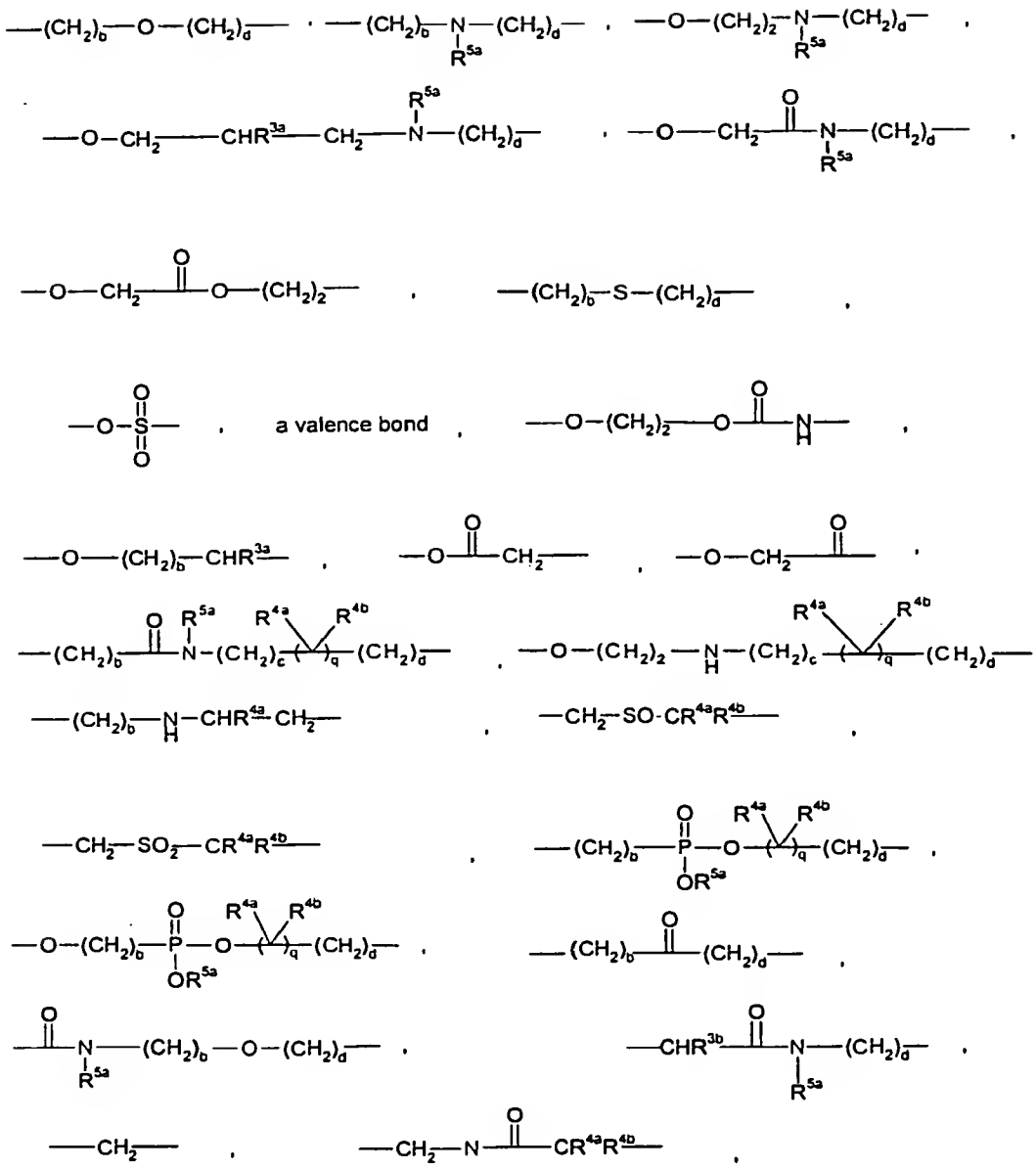


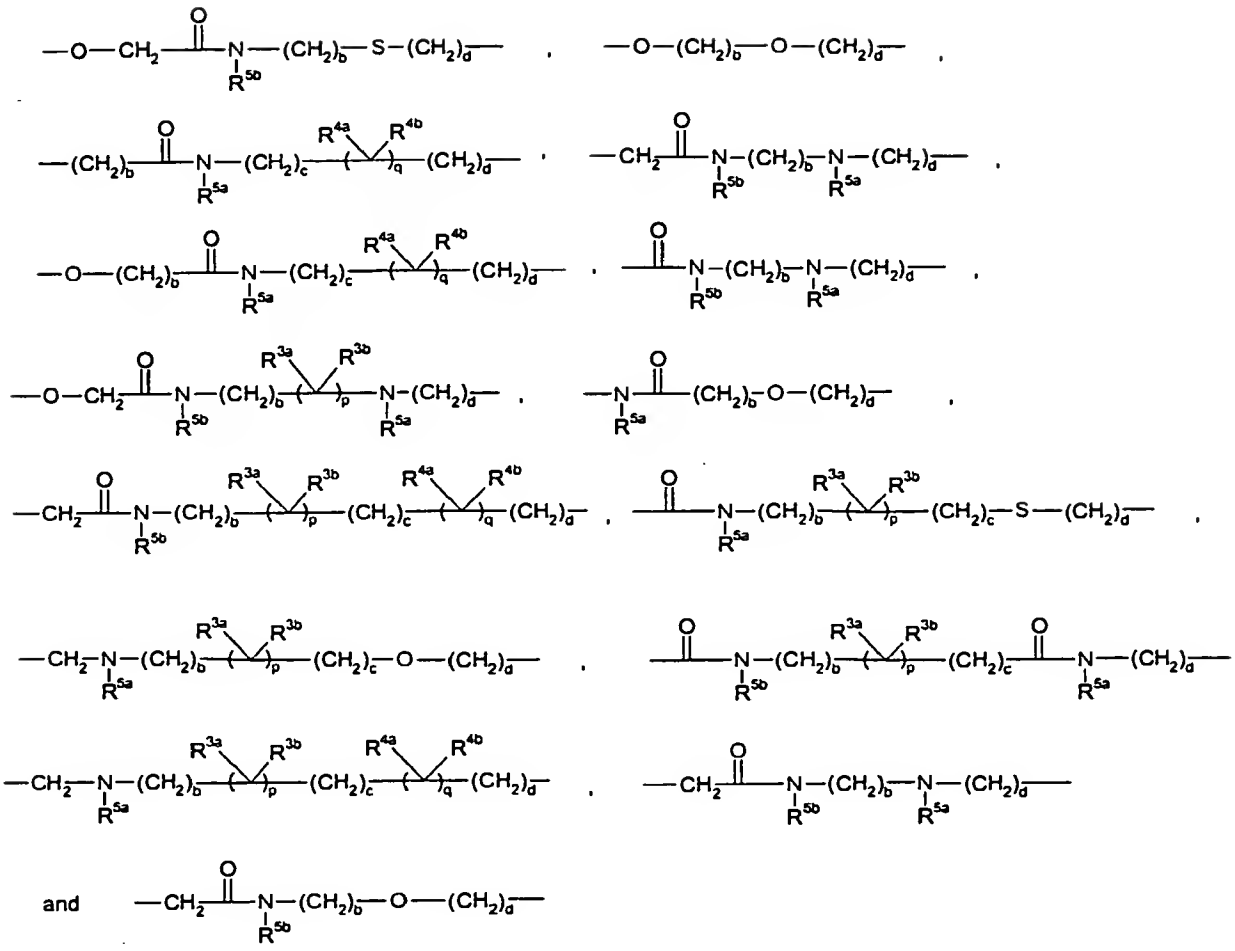


wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, a, b, c, d, p and q are as defined in claim 1.

27. A compound according to claim 26, wherein K is selected from the group consisting of





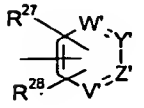
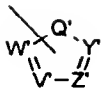
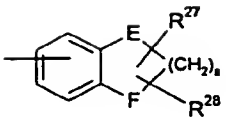
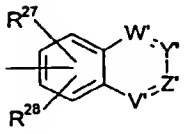
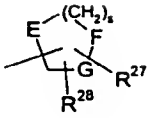
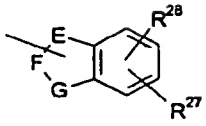
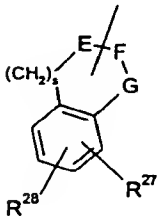
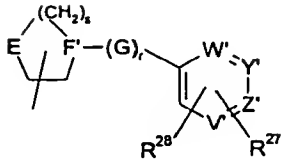
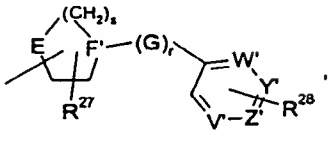
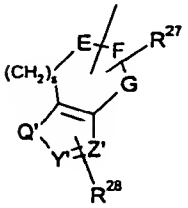
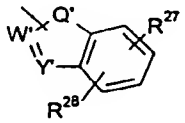
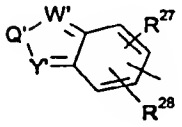
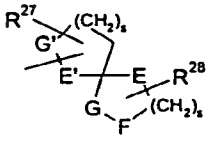


wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, b, c, d, p and q are as defined in claim 1.

29. A compound according to any one of the claims 26 to 28, wherein R^{5a} and R^{5b} independently are hydrogen, lower alkyl, -OH, $-(CH_2)_kOR^{6a}$, aryl, aryl-lower alkyl, $-CH_2CF_3$, $-(CH_2)_g-COOR^{43}$, $-COOR^{43}$, $-(CH_2)_k-CN$ or $-(CH_2)_k-NR^{6a}R^{6b}$ wherein g, k, R^{43}, R^{6a} and R^{6b} are as defined in claim 1.

30. A compound according to claim 29, wherein g and k independently are 1, 2 or 3, R^{6a} and R^{6b} independently are hydrogen, lower alkyl such as methyl or ethyl, or aryl such as phenyl,

31. A compound according to any one of the claims 26 to 30, wherein R^{3a} and R^{3b} independently are hydrogen, halogen, -OH, -O-lower alkyl, -COO-lower alkyl, lower alkyl or aryl-lower alkyl.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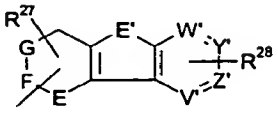
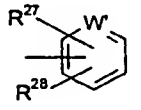
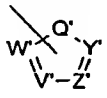
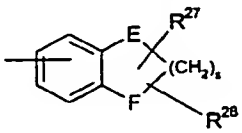
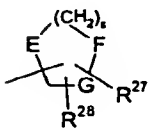
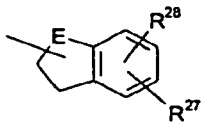
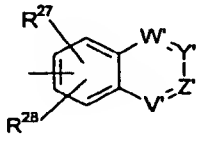


wherein s, r, R^{27}, R^{28}, V', Y', Z', Q', Z', W', E, E', F, F', G and G' are as defined in claim 1.

35. A compound according to claim 34, wherein D is hydrogen,

39. A pharmaceutical composition according to claim 38 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 1 to 36.

40. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 36.

41. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 36.

42. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 1 to 36.

43. The method according to any one of the claims 40 to 42 comprising administering to a subject in need thereof an amount of the compound as defined in claim 1 to 36 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

44. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for treating type I or type II diabetes.

45. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for treating hyperglycemia.

46. Use of a compound according to any one of the claims 1 to 36 for the manufacture of a medicament for lowering blood glucose in a mammal.

47. A compound according to any one of the claims 1 to 36 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay I or Glucagon

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00287

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 243/18, C07D 209/04, A61K 31/15, A61K 31/40
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5728646 A (NOBUHIDE TOMINAGA ET AL), 17 March 1998 (17.03.98) --	1-32
X	US 5229038 A (NOBUHIKO UCHINO ET AL), 20 July 1993 (20.07.93) --	1-32
X	EP 0451653 A2 (BAYER AG), 16 October 1991 (16.10.91) --	1-32
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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7 October 1998	13-10-1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
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